A study of the enamine character of dihydrocarbolines.

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University of Bath

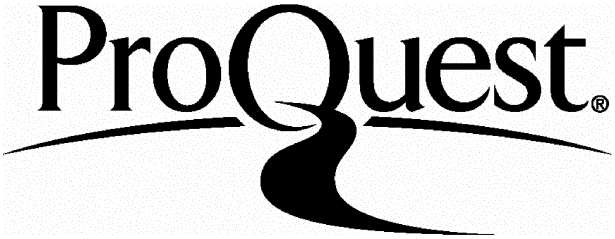
A STUDY OF THE ENAMINE CHARACTER OF DIHYDROCARBOLINES.

submitted by Kenneth Arthur CURNESS

for the degree of Ph.D.

of the University of Bath

I983



I would like to thank the academic and technical staff in the Chemistry Department of Bath University for the help, encouragement and facilities provided during the three years of my research. I would also like to thank my fellow students for making this time very enjoyable.

I must also thank my present employers for the photocopying and other facilities they have provided, and also for the encouragement I neede to complete the writing up of this thesis.

Finally I would like to thank my wife, Rosa, for her help and understanding during the protacted preparation and completion of this thesis.

SUMMARY

An attempt was made to extend the established enamine reactions of I,2-dihydroisoquinolines to the I,2-dihydro-β-carboline ring system, in the hope of preparing various 4-substituted β-carbolines for pharmacological testing. Several substituted β-carbolinium salts were prepared and subjected to attempted partial reduction to the I,2-dihydro- species, but subsequent reaction with a base and an acid halide or with an acid and an aromatic aldehyde failed to yield the required products.

Attempts to synthesise substituted β-carbolines from 2-indole-aminoacetals (via the intermediate dihydro-compound) met with more success. Cyclisation of the acetals in the presence of an aromatic aldehyde and an acid gave the requred product in two out of four cases. A larger range of aldehydes were not investigated.

An investigation was carried out into the cyclisation of 3-indole-aminoacetals to γ-carbolines. The results obtained were at variance with the published data, but no firm conclusions could be made concerning the cause of the discrepancies.

Although only moderately successful in its original aims, the work described in this thesis led to the synthesis of several new carboline and indole derivatives and provided two possible routes to 4-substituted-β-carbolines.

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INTRODUCTION

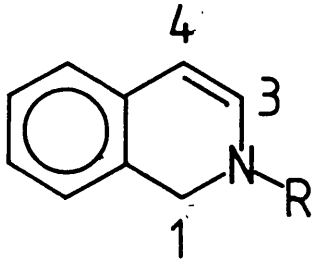
During the course of studies into the enamine character of I,2-dihydroisoquinolines (I) carried out at the School of Chemistry of Bath University[I], several methods were established for the synthesis of important isoquinoline alkaloids, and in addition, many novel isoquinoline derivatives were prepared, especially those substituded at the C-3 and/or C-4 positions. It was also shown that I,2-dihydroisoquinolines are useful synthetic intermediates for a variety of novel ring systems.

The chemical rationale for the research reported in this thesis is that the above mentioned chemistry could be applied to dihydrocarbolines (2) and (3) which might provide the templates for molecules of biological interest. The academic interest in the project lies in the fact that such structures are novel and contain <u>two</u> enamine systems. Thus interactions (if any) between the two could be studied, and competitive reaction profiles examined. In addition the allyl and benzyl migration reactions discovered in the isoquinoline series ought not to be unique to that system , and it is important to study these rearrangements in other heterocyclic enamines.

In order to fulfil these aims it was necessary to develop synthetic methods for the preparation of dihydrocarbolines (2) and (3) based upon previous extensive experience with I,2-dihydroisoquinolines.

The research was supported by a CASE award financed

jointly by the Science Research Council and Allen & Hanburys Research Ltd. now Glaxo Group Research Ltd. The interest for the pharmaceutical concern is that almost all indoles and carbolines, that had been tested previously, possed some biological activity. The chemical research would produce a range of substituted carbolines for pharmacological evaluation, particularly against the symptoms and causes of migraine.



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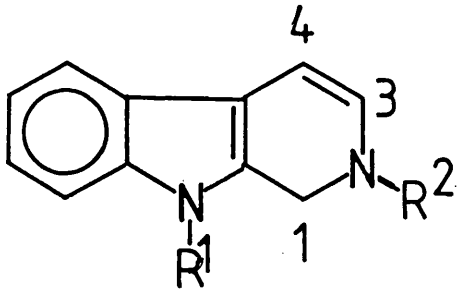

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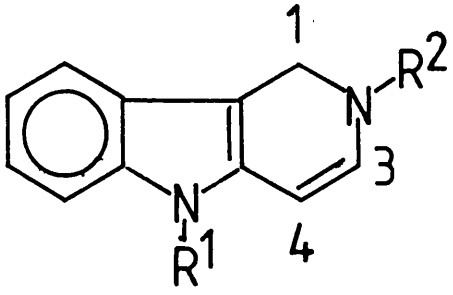


(3)

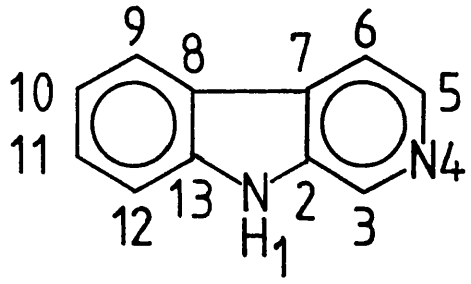
Nomenclature of the Carboline Ring System.

The nomenclature used to describe the fused benzene-pyrrole-pyridine ring system has been repeatedly modified since Perkin and Robinson[2] introduced the name carboline for this tricyclic unit encountered for the first time in the Harmala alkaloids. In the earliest version of carboline nomenclature the parent compound of the series, the trivial name of which is norhaman, was referred to as 4-carboline and numbered as in structure (4). The subsequently discovered isomers of this ring system, differing only in the position of the nitrogen atom in the pyridine ring, were therefore designated 3-, 5- and 6-carbolines.

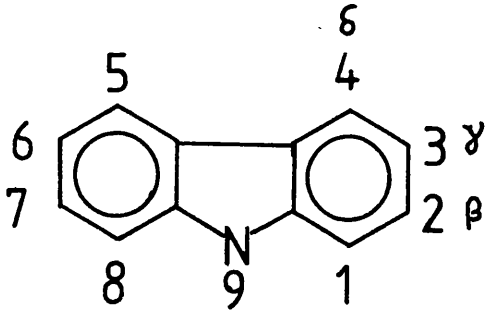
The numbering of the carboline system was later modified[3] to that shown in the part structure (5), and the position of the basic nitrogen atom in the pyridine ring designated by a Greek letter. The same system of numbering has been used without the Greek letter.[4,5]

According to the "Ring Index"[6] the systems are classified as pyridoindoles, thus α-carboline (6) becomes 9H-pyrido[2,3-b]indole, β-carboline (7) becomes 9H-pyrido[3,4-b]indole, γ-carboline (8) is 5H-pyrido[4,3-b]-indole and δ-carboline (9) is 5H-pyrido[3,2-b]indole. The systems are numbered as shown in structures (6) - (9).

This convention is now generally accepted[7,8] although


9
8
7
6
10
5
11
N4
13
N
2
12
3
H1

(4)


δ
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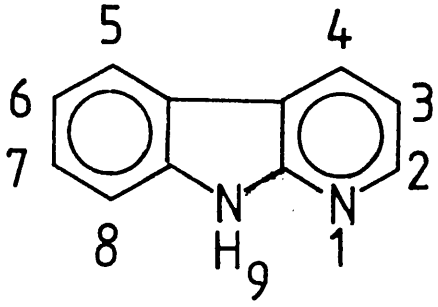
4
6
3 γ
7
2 β
N
8
9
1
α

(5)


5
4
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2
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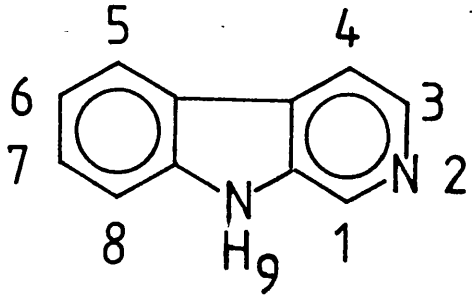
H9
1

(6)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N 2
N
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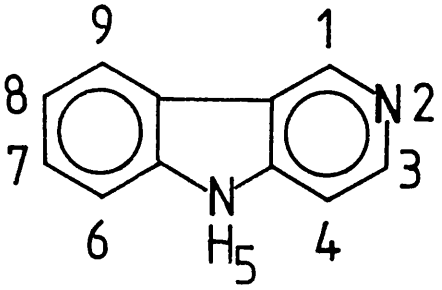
H9
1

(7)


9
1
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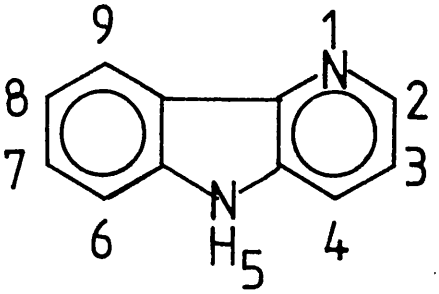
N 2
7
3
N
6
H5
4

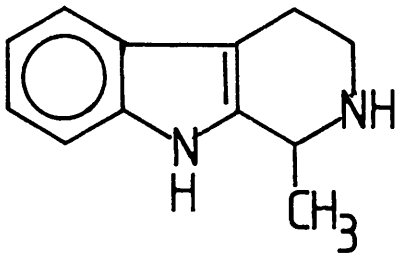
(8)


9
1
N
8
2
7
3
N
6
H5
4

(9)

the older Greek notation still finds its way into the chemical literature, especially because of its brevity and wide general use. It seems superfluous to argue the case for further change but other variants have occurred and are still to be found in the literature. β-Carboline has been referred to as 4-carbazoline[2,3] and also as 2,9-diazafluorene, its I-methyl-I,2,3,4-tetrahydro-derivative (IO) has been called I-methyltryptoline[9] and α-carboline has been sold commercially as I-azacarbazole. The trivial norharman nomenclature, in conjunction with numbering as in (4)[IO,II] or as in (7) is still to be found in recent papers.

In this thesis the carboline rather than the strictly accurate pyridoindole nomenclature will be adopted supplemented by the numbering of ring atoms as shown in structures (6) to (9). Anhydro-bases (e.g. (II)) derived from quaternary carbolinium salts will be referred to as such and not as isocarbolines[2,3] or γ-carbolines.[I2]



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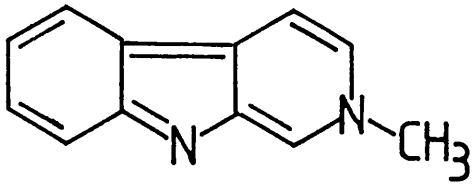


(11)

Occurrence and Biogenesis of Simple Carbolines in Plants.

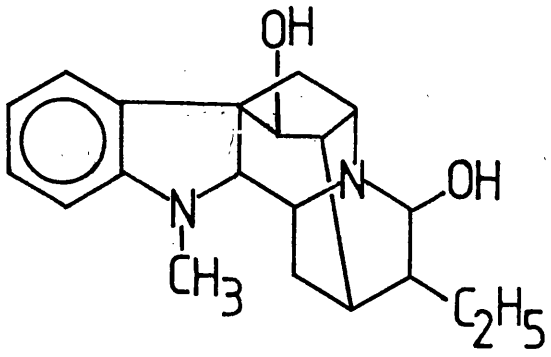
The origins of the carbolines[11,13,14,15] have been discussed in many texts on alkaloid biosynthesis but a brief summary is necessary here because these reviews represent a fragmentary view of the subject. Several of the currently used classifications of indole alkaloids, for example, those of Boit,[16] Hesse[17] and Kompis et al.[14] place carboline compounds in different sub-groups. Another factor is that the majority of the work on carbolines has been concerned with the biosynthesis of the third and fourth rings of more complex alkaloids, such as ajmaline (I2) and yohimbine (I3). These discussions lie outside the scope of this thesis which is concerned with simple carbolines containing the basic three ring skeleton.

Studies directed towards the occurrence and biogenesis of carbolines are almost exclusively concerned with the β-carboline ring system, numerous derivatives of which are widely distributed in nature primarily in the form of tetrahydro- derivatives. Considerably fewer compounds with totally aromatic structures are known - approximately 2% of all indole alkaloids reported so far.

Alkaloids based on the α-carboline or γ-carboline ring systems have not been detected in living systems although an α-carboline has been isolated from coal tar

oil.[18] Although simple δ-carbolines do not occur in nature, benzo- derivatives such as crytolepine (I4) have been isolated from plant sources[19] and will be discussed in more detail later on in this section.

Tables I, 2 and 3 list the substitution paterns and trivial names of the fully aromatic, I,2,3,4-tetrahydro- and 3,4-dihydro-β-carbolines so far found in plants. Whereas table 4 lists some of the naturally occurring β-carbolines carrying more complex substituents. Table 5 provides a summary of the plant families and genera which metabolise β-carbolines. Such a survey is in no way exhaustive, but gives some idea how widely distributed the β-carboline ring system is in nature.



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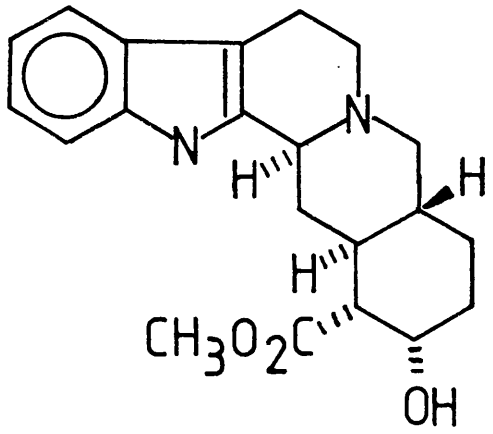

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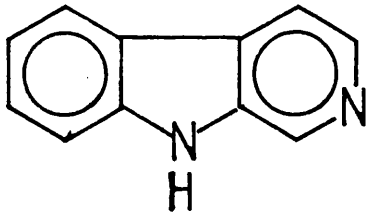

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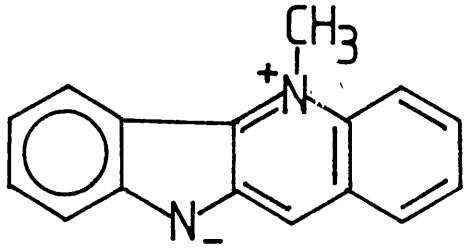
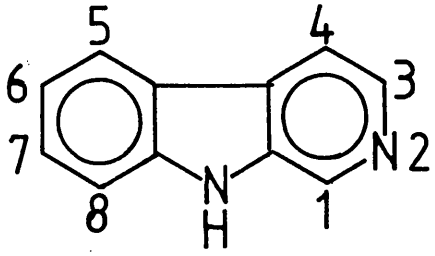


(14)

TABLE I. Naturally Occurring Aromatic β-Carbolines.



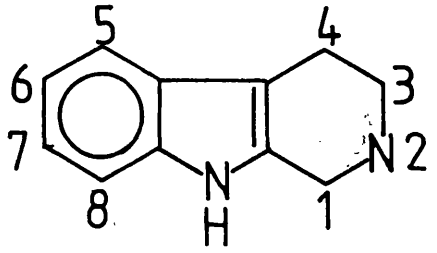
TRIVIAL NAME		SUBSTITUTION				
		C-I	C-3	C-4	C-7	OTHER
(7)	Norharman	---	---	---	---	---
(I5)	Harman	CH_3	---	---	---	---
(I6)	Harmanine	CH_3	---	---	---	N-2→O
(I7)	Harmol	CH_3	---	---	OH	---
(I8)		CH_3	---	---	---	C-6,CH_3O
(I9)	Harmine	CH_3	---	---	CH_3O	---
(20)	Harmine-N-Oxide	CH_3	---	---	CH_3O	N-2→O
(2I)		CH_2OH	---	---	---	---
(22)	Harman-3-Acid	CH_3	CO_2H	---	---	---
(23)		CO_2CH_3	---	---	CH_3O	---
(24)		CO_2CH_3	---	---	---	---
(25)		$CO_2C_2H_5$	---	---	---	---
(26)		$COCH_3$	CO_2CH_3	---	---	---
(27)		CH_3	CO_2CH_3	---	---	---
(28)		$COCH_3$	---	CH_3O	---	---
(29)	Crenatine	C_2H_5	---	CH_3O	---	---
(30)		$CONH_2$	---	---	CH_3O	---

TABLE I cont.

		C-1	C-3	C-4	C-7	OTHER
(31)	Crenatidine	C_2H_5	---	CH_3O	---	C-8,CH_3O
(32)		$CONH_2$	---	---	---	---
(33)		---	---	---	CO_2CH_3	---
(34)		$COCH_3$	---	---	CH_3O	---
(35)	Pavettine	$CH=CH_2$	---	---	---	---
(36)		$COCH_3$	---	---	---	---
(37)	Dehydro-crenatine	$CH=CH_2$	---	CH_3O	---	---
(38)	Dehydro-crenatidine	$CH=CH_2$	---	CH_3O	---	C-8,CH_3O
(39)		$CH=CH_2$	---	CH_3O	CH_3O	---
(40)	Ruine	CH_3	---	---	CH_3O	C-8,OGlu[a]
(41)	Melonine F	CH_3	---	---	---	N-2$^+$,CH_3
(42)		---	---	---	---	N-2$^+$,CH_3
(43)		CH_2CH_2OH	---	CH_3O	---	---
(44)		$\underset{\underset{OH}{\vert}}{CH}CH_2OH$	---	CH_3O	---	---
(45)		CHO	---	---	---	---

a) OGlu = Glucosyloxy

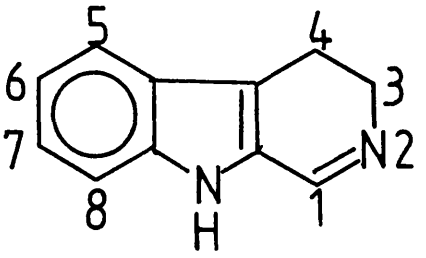
TABLE 2. Naturally Occurring Tetrahydro-β-carbolines.



TRIVIAL NAME	SUBSTITUTION				
	C-I	N-2	C-6	C-7	OTHER
(46) Eleagnine	CH_3	---	---	---	---
(47) Tetrahydroharmol	CH_3	---	---	OH	---
(48)	CH_3	CH_3	---	OH	---
(49) Leptaflorine	CH_3	---	---	CH_3O	---
(50) Leptocladine	CH_3	CH_3	---	---	---
(51)	---	CH_3	CH_3O	---	---
(52)	---	---	---	---	C-3,CH_3
(53)	---	CH_3	---	---	---
(54)	CH_3	---	CH_3O	---	---
(55)	---	CH_3	CH_3O	---	N-9,CH_3
(56)	CH_3	CH_3	CH_3O	---	---
(57) Plectocomine	---	---	OH	---	---
(58) Shepherdine	CH_3	---	OH	---	---
(59)	i-Bu[a]	---	---	---	---
(60)	CH_3	---	---	---	C-5,CH_3O

a) i-Bu = isobutyl

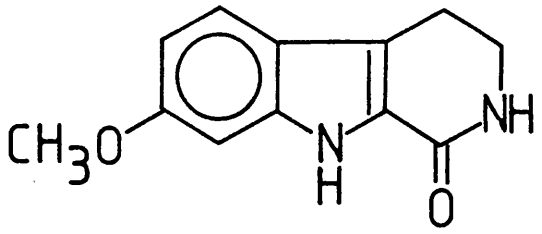
TABLE 3. Naturally Occurring 3,4-Dihydro-β-carbolines.



(61) Harmalol	CH_3	---	OH	---
(62) Harmaline	CH_3	---	CH_3O	---
(63)	CH_3	CH_3O	---	---
(64) Dihydroruine	CH_3	---	---	C-8,OGlu[a]
(65)	---	---	---	N-9,$COCH_3$

a) OGlu = Glucosyloxy

TABLE 4. Naturally Occurring β-Carbolines Carrying More Complex Substituents.



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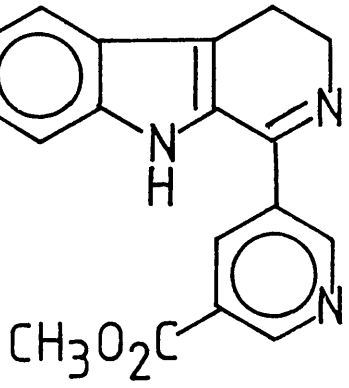

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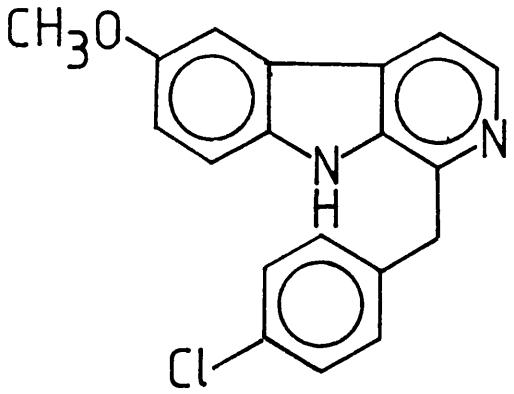

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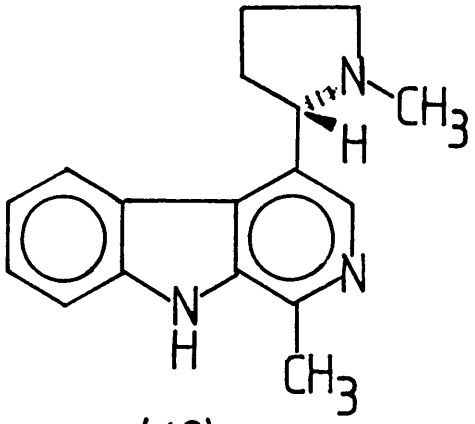

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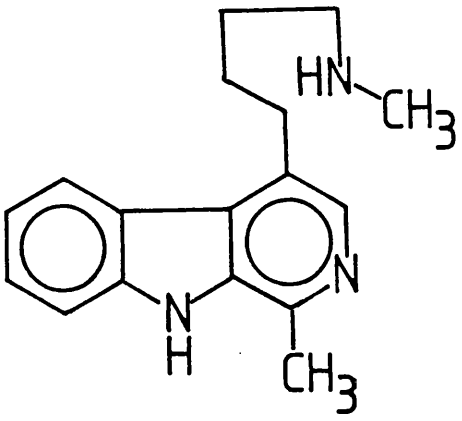

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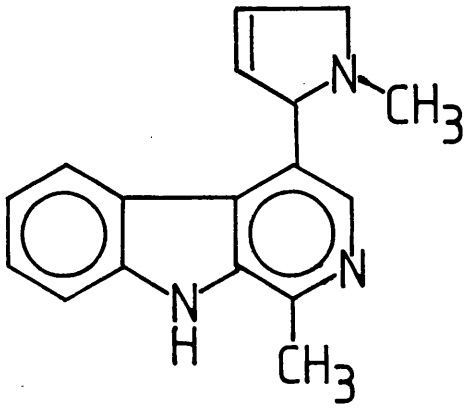

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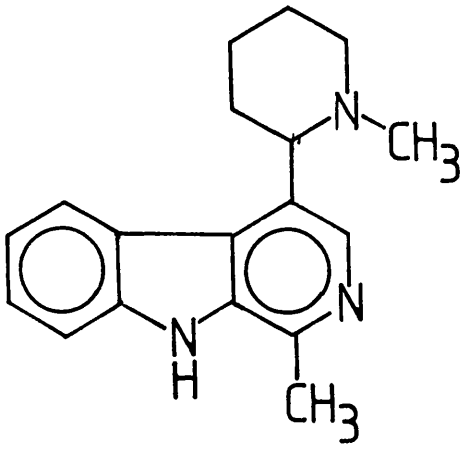

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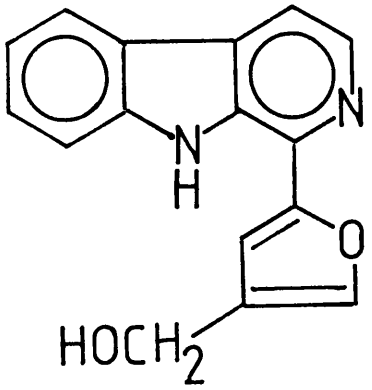

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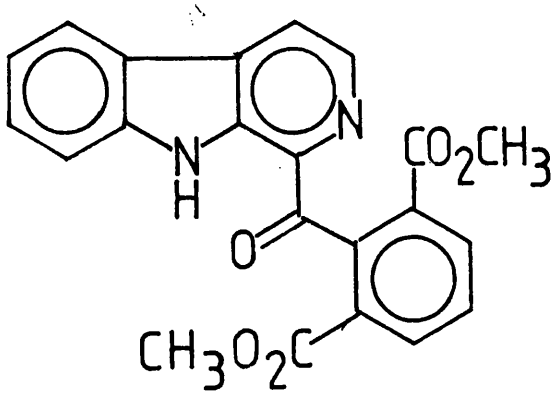

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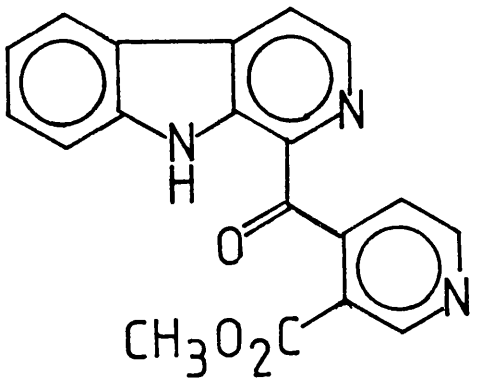

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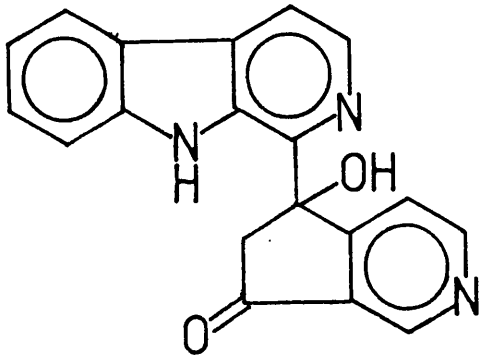

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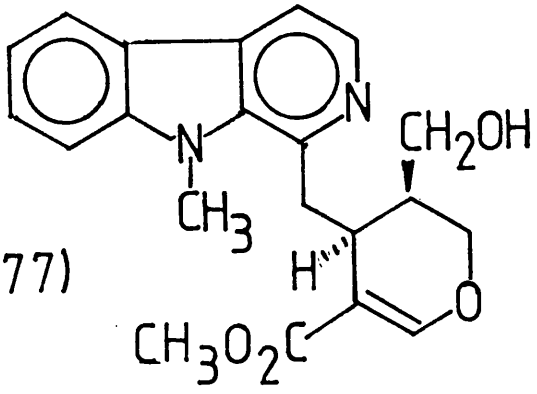

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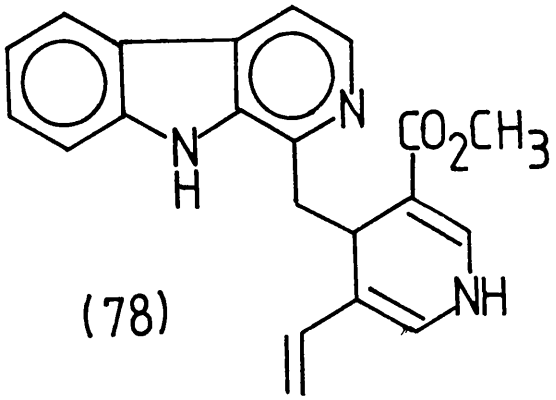

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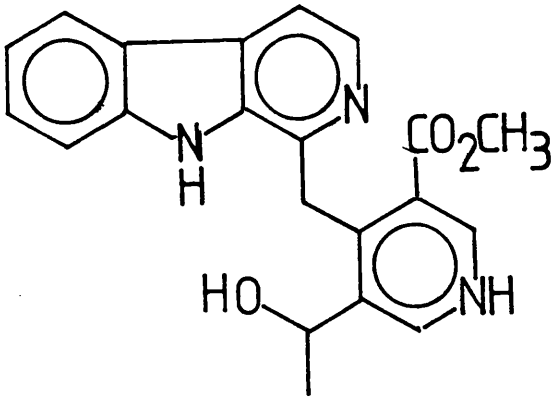

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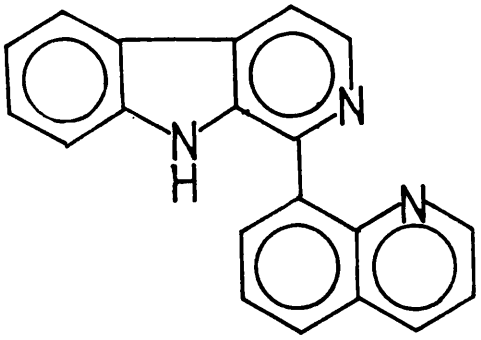

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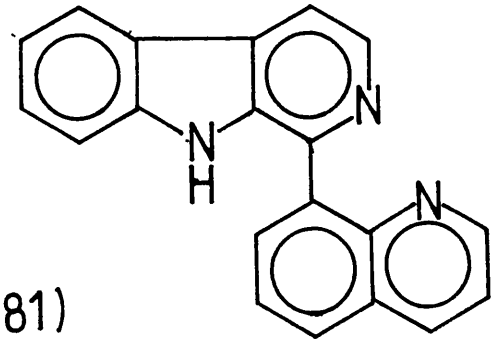


(81)

TABLE 5. Occurrence of β-Carbolines.

Family and Genus	Alkaloid(s)	Reference(s)
ACANTHACEAE		
Adhatoda vasica	65	I9
APOCYNACEAE		
Aspidosperma exalatum	22	II
A.polyneuron	22	I3
Alstonia constricta	74,77	II
Ochrosia nakaiana	I5	2I
Rauwolfia psychotriodes	I5	22
Pleiocarpa mutica	24,33	23
ARACEAE		
Pinellia pedatisecta	7	24
BIGNONIACEAE		
Newbouldia laevis	I5	25
CALYCANTHACEAE		
Calycanthus sp.	I5,I9	II
CHENOPODIACEAE		
Arthrophytum leptocladum	50,53	25,26
Hammada leptoclada	46,50,52	I3,25

TABLE 5 cont.

Family and Genus	Alkaloid(s)	Reference(s)
CHENOPODIACEAE cont.		
Kochia soparia	I5,I9	28
COMBRETACEAE		
Guiera sengalensis	I5,46	29
CYPERACEAE		
Carex sp.	I5	25
C.brevicollis	I5,I7,69, 70,7I,72	I3,25,30,3I
C.parva	69,70	32
ELEAGNACEAE		
Eleagnus angustifolia	46,47,48	I3
E.commutata	59	33
Sherpherdia argentia	47	34
S.canadensis	47,58	34
GRAMINEAE		
Lolium perenne	I5,7I	II,35
Phalaris arundinaceae	5I,55,56	36,37,38
P.aquatica	46,5I,53	35
P.tuberosa	5I,53	26

TABLE 5 cont.

Family and Genus	Alkaloid(s)	Reference(s)
LAURACEAE		
Aniba santalodora	68	27
Nectandra megapotamica	5I	38
LEGUMINOSAE		
Abraribra rubra	I5	II
Acacia baileyana	46	39
A.complanata	46,50	40
A.simplicifolia	53	4I
Anandenanthera peregrina	53,56	26,35,42
Desmodium gangeticum	4I,42	II,43
Prosopis nigra	I5,46	44
Pentalostyles labicheoides	46	45
LOGANIACEAE		
Strychnos melinoniana	4I	II
MALPIGHIACEAE		
Banisteriopsis argentea	46,60	46
B.caapii	9,20,23, 30,34,49, 62,64	I3,46,47,48
B.inebrans	I7,I9,20, 49,62	II,49

TABLE 5 cont.

Family and Genus	Alkaloid(s)	Reference(s)
MALPIGHIACEAE cont.		
Banisteriopsis rusbyara	53	26
Banisteria lutea	I9	II
Caabi parcensis	I9	II
MYRISTICAEAE		
Gymacranthera paniculata	53	26
Virola cuspidata	I8,54	50
V.rufula	5I	26,42,50
V.theiodora	46,5I,53,63	26,42,50
PALMAE		
Plectocomiopsis geminiflorus	57	5I
PAPAVERACEAE		
Meconopsis nupaulensis	5I	52
M.rudis	5I	53
PASSIFLORACEAE		
Passiflora edulis	I5,I7,I9,62	II,55
P.incarnata	I5,I7,I9, 6I,62	II,I3

TABLE 5 cont.

Family and Genus	Alkaloid(s)	Reference(s)
PASSIFLORACEAE cont.		
Passiflora actinea, P.alba, P.alata, P.bryoniodes, P.capsularis, P.eichleriana, P.quadrangularis, P.ruberosa	I5	II
P.coerulae, P.decaisneana, P.foetida, P.warnergii, P.subpeltata	I5	54
POLYGONACEAE		
Calligonium eripodum	I5,I6	II
C.minimum	I5,I6,46	II,I3
RUBIACEAE		
Leptactina densiflora	46,49	II
Nauclea diderrichii	I5,24,27 32[a],67	56,57,58
Ophiorrhiza japonica	I5	II
Palicourea alpina	I5	II
Pauridiantha callicarpoides	15,75,76	II
P.lyalli	I5,78,79	59,60
Pavetta laneolata	35	II
Psychotria virides	53	48

TABLE 5 cont.

Family and Genus	Alkaloid(s)	Reference(s)
RUBIACEAE cont.		
Sickingia rubra	I5	II
Simira klugii	I5	II
Uncaria sp.	I5,I9,62	6I,62
RUTACEAE		
Perganum harmala	I7,I9,40, 6I,62,64	II,I3,63,64
SIMAROUBACEAE		
Ailanthus altissima	28,43,44	65,66
A.malabarica	24,28,29,3I, 32[b],36,37,38	65,66,II
Perriera madagascarlensis	38,39	II
Picrasma ailanthoides	2I,24,25, 38,45	67,68
P.crenata	24,29,3I,33	II,69
P.javicana	29,37	70
SOLANACEAE		
Vestia lyciodes	26	7I
SYMPLOCACEAE		
Symplocus racemosa	I5	72

TABLE 5 cont.

Family and Genus	Alkaloid(s)	Reference(s)
ZYGOPHYLLACEAE		
Nitaria komarovii	80,8I	73
Tribulus terrestris	I5,I9	I3
Zygophyllum fabago	I5,I7,I9	I3

Notes:

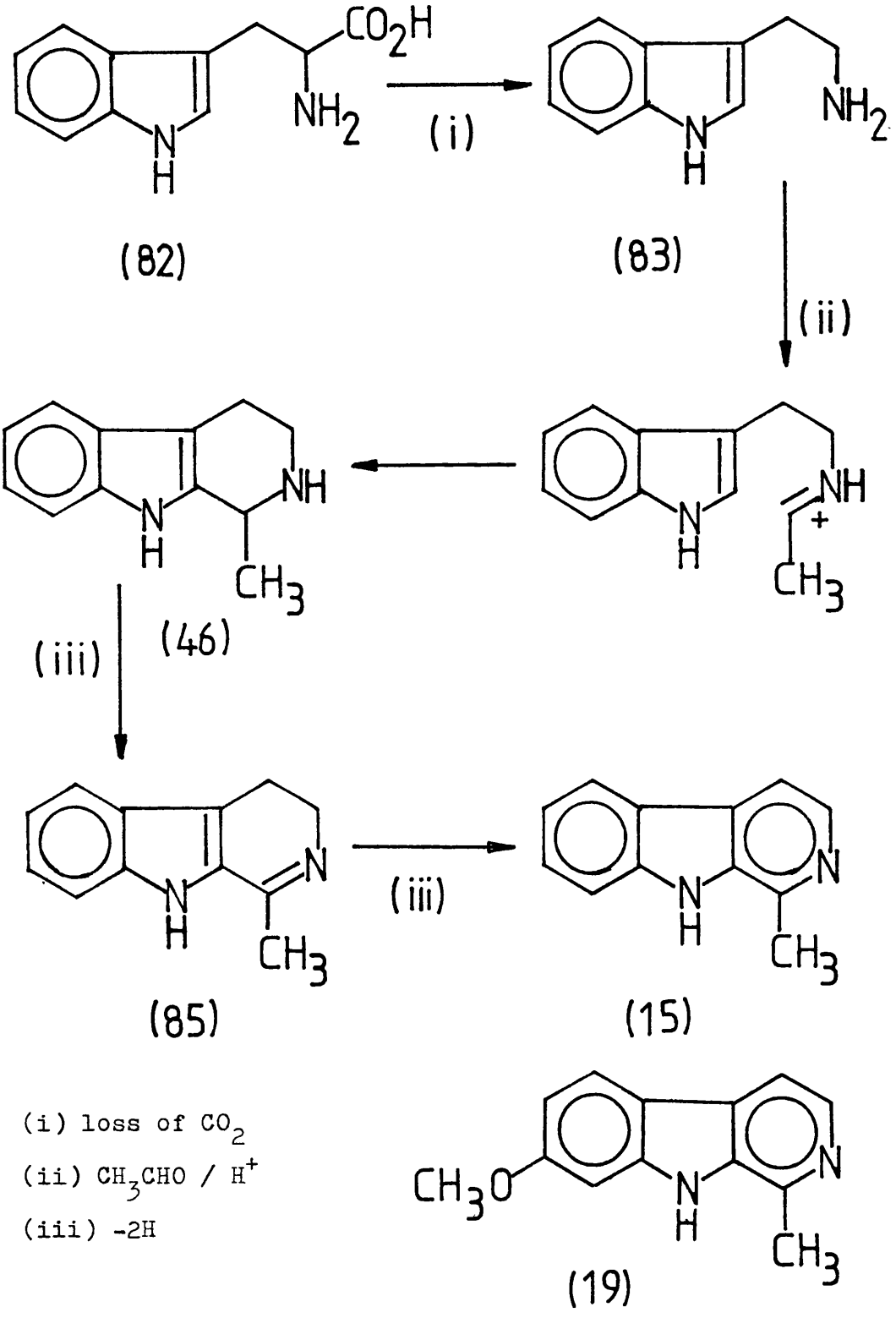
a) This compound could possibly be an artifact formed by the use of ammonia in the extraction sequence.

b) The use of ammonia was avoided and this compound is not an artifact.

A number of schemes have been proposed to account for the biogenesis of β-carbolines, the first of which, developed by Perkin and Robinson,[74] suggested that the skeleton of these molecules could be formed from tryptophan (82) (after decarboxylation to tryptamine (83)) and a two or three carbon fragment such as acetaldehyde then added. In support of this scheme it was shown[75] that I-methyl-I,2,3,4-tetrahydro-β-carboline (46) can be readily synthesised from tryptamine and acetaldehyde in dilute aqueous solution at 25°C, using an acetate (pH 5.2) or phosphate (pH 6.2) buffer - so called physiological conditions. This sequence is outlined in Scheme I.

How the two or three carbon fragments combine with tryptamine to form the alkaloids has been a subject of continuing speculation mainly because the great metabolic activity of compounds such as acetate, acetaldehyde and pyruvate make it very difficult to obtain unambiguous results from classical feeding experiments. For example $^{14}CH_3COOH$ fed to Eleagnus angustifolia led to specific incorporation of the label into the C-I position of I-methyl-I,2,3,4-tetrahydro-β-carboline (46).[76] In contrast, when radioactive acetate was fed to Perganum harmala[77] it led to an apparent randomisation of the label in the 7-methoxy-I-methyl-β-carboline (I9) formed. However the feeding of pyruvate to this plant was claimed[78] to lead to significant specific incorporation of the label into the same metabolite.

Scheme I.


CO2H
NH2
(i)
NH2
(82)
(83)
(ii)
NH
CH3
(46)
(iii)
N
CH3
(85)
(iii)
(15)
CH3O
(19)
(i) loss of CO2
(ii) CH3CHO / H+
(iii) -2H

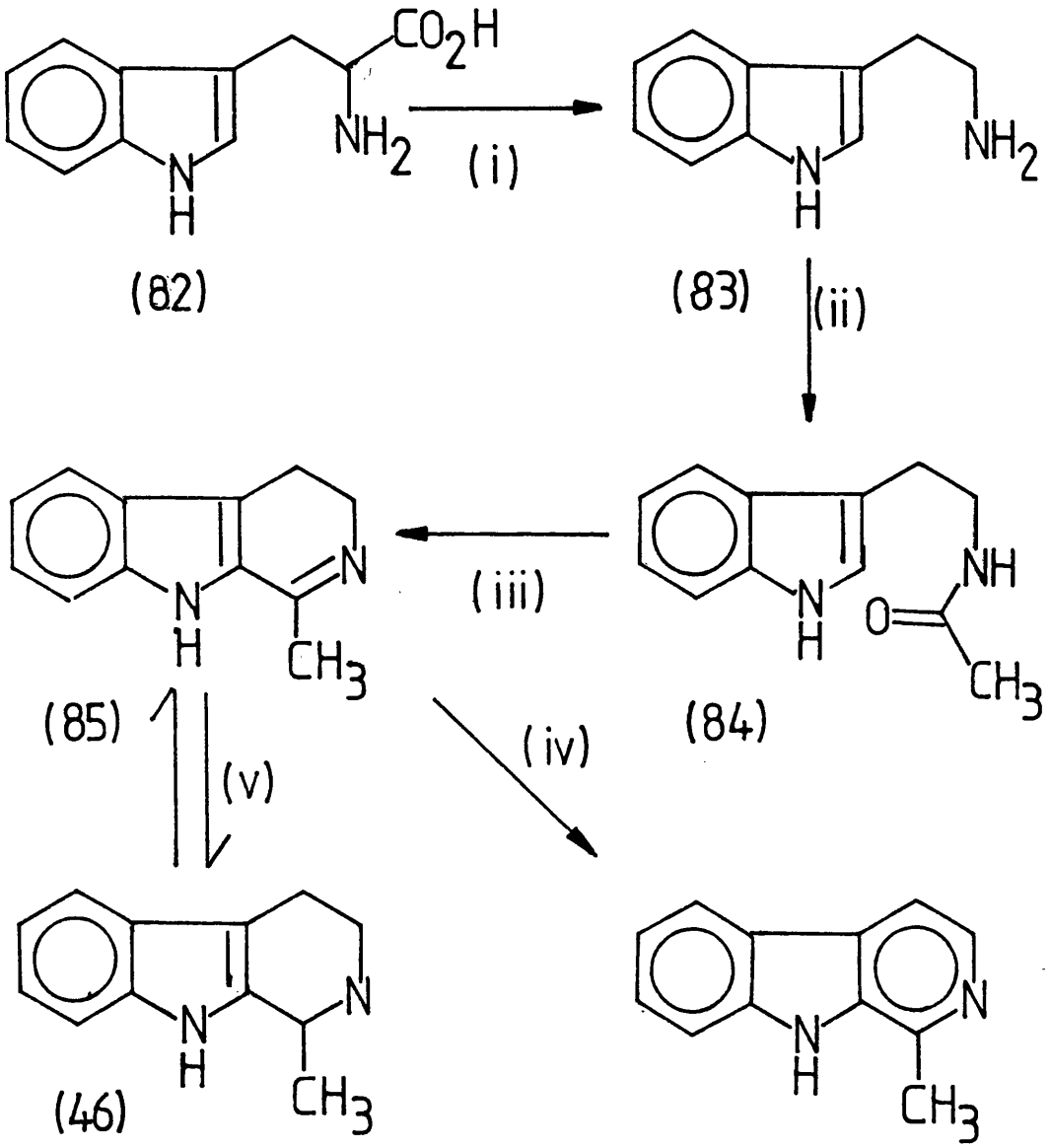
From related studies with Passiflora edulis, Slaytor and McFarlane[79] proposed an alternative route to the biosynthesis of β-carbolines in which the ring system, in this case harman (I5), is formed by cyclic dehydration of N-acetyltryptamine (84) which is itself formed by N-acetylation of tryptamine (derived from tryptophan) with presumably acetyl-coenzyme-A (CH_3CO-SCoA). This sequence is outlined in Scheme 2.

Harmalan (85) could not be detected in P.edulis and, although labelled harmalan was converted to labelled harman, it could not be conclusively shown that it was an intermediate in the biosynthesis of harman.

The essential difference between the scheme of Perkin and Robinson and Slaytor and McFarlane is that in the latter the first tricyclic intermediate is harmalan (85) and not eleagnine (46). However, eleagnine was converted to harmalan and thence to harman (I5) in P.edulis suggesting an in vivo system involving two succesive dehydrogenations. Eleagnine could not be detected in P.edulis but the fact that tetrahydro-β-carbolines occur in a number of plants which produce both dihydro- and fully aromatic β-carboline alkaloids[I6] led these authors to claim that their biogenetic scheme was correct.

In order to provide further support for their proposals, Slaytor and McFarlane sought to prove that

Scheme 2.



(i) $-CO_2$

(ii) CH_3CO-SCoA

(iii) $-H_2O$

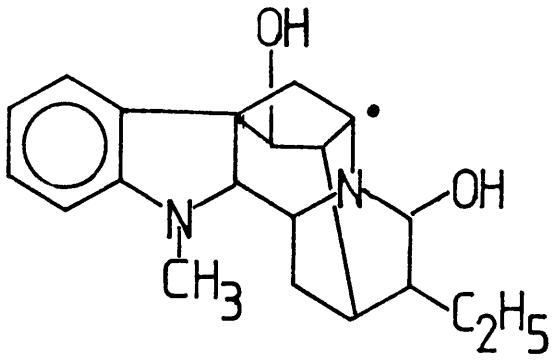
(iv) $-2H$

(v) $+2H$

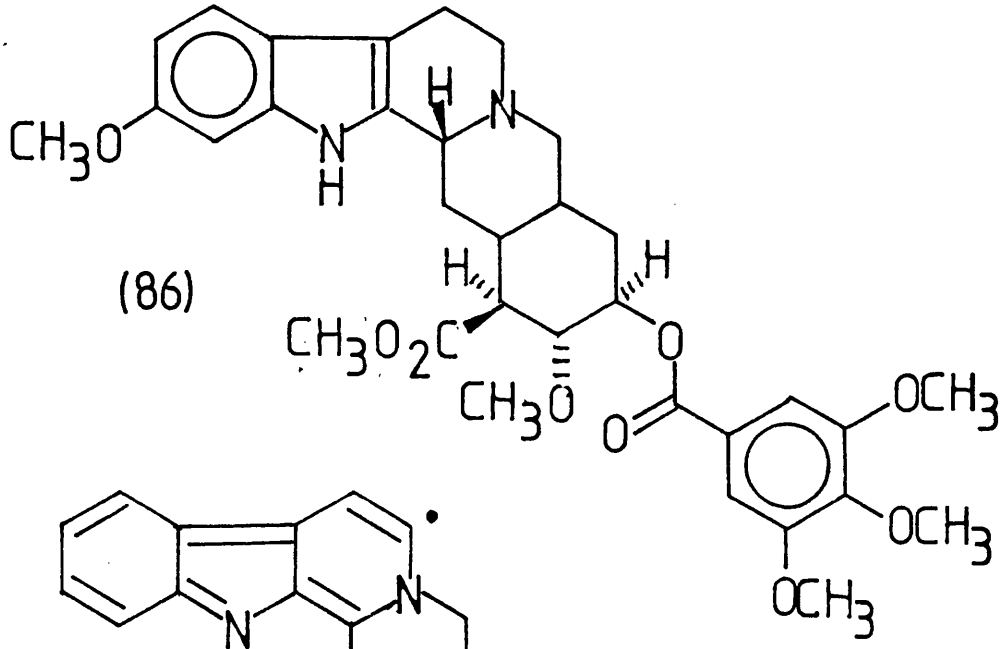
N-acetyltryptamines were the precursors to eleagnine (46) in Eleagnus angustifolia.[80] Feeding experiments showed no incorporation of label into eleagnine showing that N-acetylamines are not involved in the biosynthesis of tetrahydro-β-carbolines, although there always remains the possibility that the amides are not reaching the site of synthesis. It is therefore possible that N-acetylamines are involved only in tne biosynthesis of fully aromatic β-carbolines and that separate pathways are operating in those plants where aromatic β-carbolines and tetrahydro-β-carbolines occur together. An alternative explanation for the co-occurrence is that aromatic β-carbolines are autooxidation products of the tetrahydro-β-carbolines and are artifacts of extraction, an argument loosely supported by the fact that there is no reported co-occurrence of tetrahydroisoquinolines and isoquinolines.

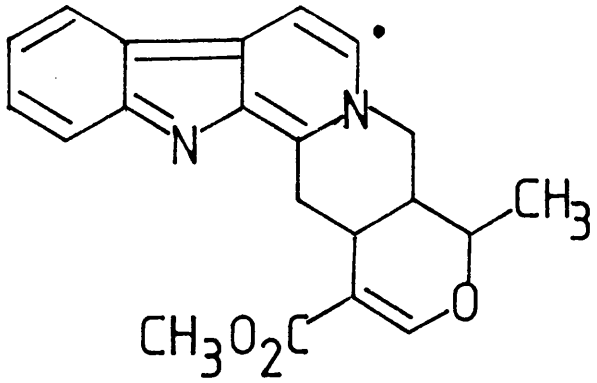
From the above evidence it can be seen that even now there is not a clear understanding of the detailed steps involved in the biosynthesis of β-carboline alkaloids yet there is a great deal of experimental evidence to suggest that the general proposals outlined by Perkin and Robinson and Slaytor and McFarlane[74,80] are correct. Radioactive ajmaline (12),[81] reserpine (86)[81] serpentine (87),[81,82] vindoline (88)[83,84] and ibogaine (89)[85] were obtained from radioactive tryptophan and degradations indicated that the alkaloids were labelled in the expected positions.

(12)

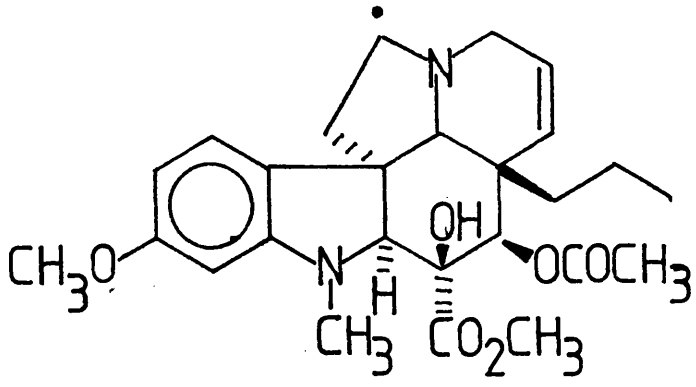

OH
N
OH
N
CH3
C2H5

(86)


CH3O
N
H
H
N
H
H
CH3O2C
CH3O
O
O
OCH3
OCH3
OCH3

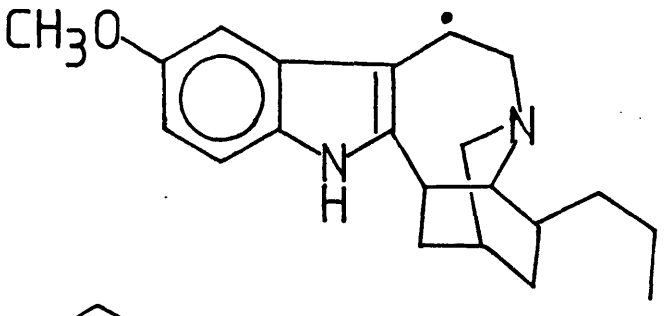

N
N
CH3
O
CH3O2C

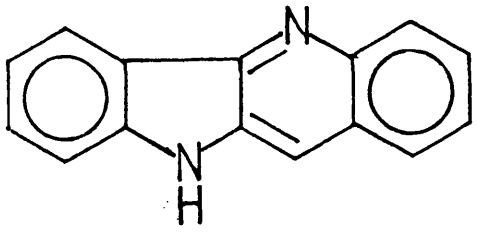
(87)



(88)

(89)





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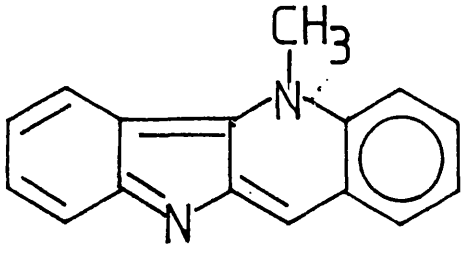

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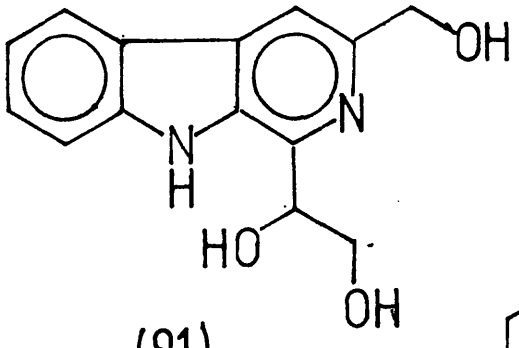

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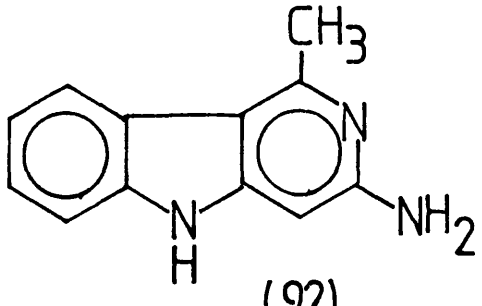


(92)

The only divergent opinion concerning the biosynthetic origin of β-carboline alkaloids is that of Wenkert,[86] who postulates that the alkaloids are derived directly from carbohydrate precursors by way of an anthranilic acid - erythrose derived intermediate and not by way of tryptophan or tryptamine. This interesting alternative hypothesis, which is based almost entirely on structural arguments, was put forward as one aspect of a general carbohydrate hypothesis of alkaloid biogenesis. In a few cases where the alternative theories are amenable to direct experimental test[87,88] the carbohydrate hypothesis was not substantiated. Whether or not it is applicable to the biogenesis of β-carbolines has never been studied.

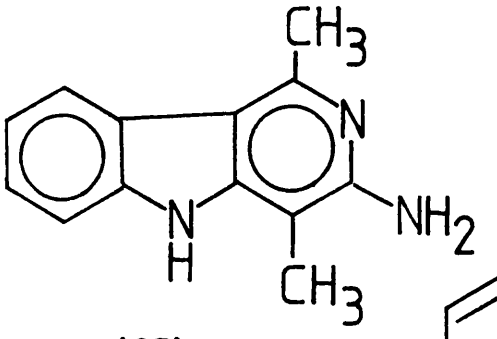
As previously indicated, the only other carboline alkaloid which occurs in nature is the benz-δ-carboline derivative, crytolepine (I4). This alkaloid has been isolated from the roots of Crytolepis triangularis[88] and C.sanguinolenta[89] (Asclopidaceae) and the structure (I4) was assigned from chemical evidence and its spectral similarity to the known base quindoline (90). Two alternative biogenetic schemes have been proposed, one is based on tryptophan and 2-methylaminobenzaldehyde[90] and the other based on an anthranilic acid - erythrose adduct and a second anthranilic acid unit.[86]

The hydroxylated β-carboline derivative pyridindol

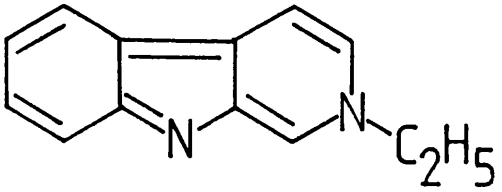
(9I) has recently been isolated from the bacteria Streptomyces alboverticillatus[9I,92] and has antibiotic properties. This is so far the only β-carboline isolated from a bacterial source, Norharman (7) and harman (I5) have been detected in the marine organism Noctiluca miliaris.[93] This is so far the only record of a carboline occurring in a marine species.

Various carboline derivatives at differing oxidation levels have been isolated as artifacts from a number of natural sources. Two highly mutagenic compounds isolated from the smoke - condensates of tryptophan pyrolosis were shown to be 3-amino-I-methyl-γ-carboline (92) and 3-amino-I,4-dimethyl-γ-carboline (93).[94,95] Norharman (7) and harman (I5) have been found in marihuana smoke[96] and harman and 2-ethyl-β-carboline (94) have been obtained from tobacco smoke - condensates.[97,98]

Numerous carbolines have been detected in the tar residue from the pyrolosis of sardines, and have turned out to be fungicidal and fugistatic in action.[99]



(93)

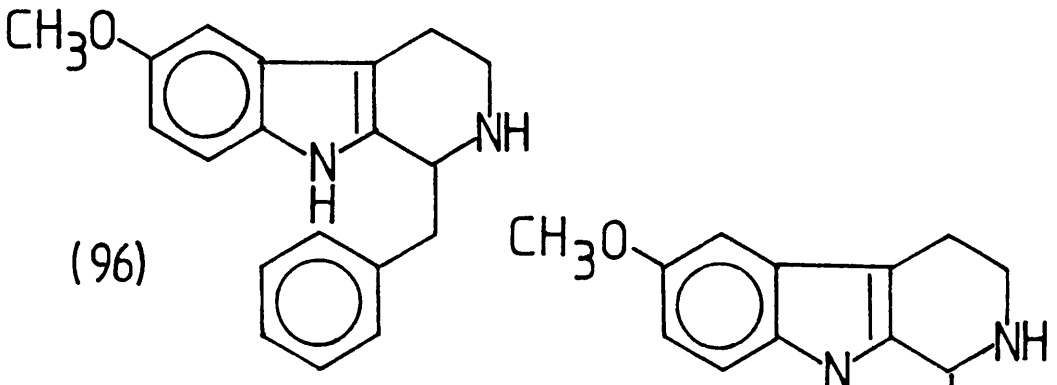


(94)

Occurrence of Simple Carbolines in Mammalian Tissue.

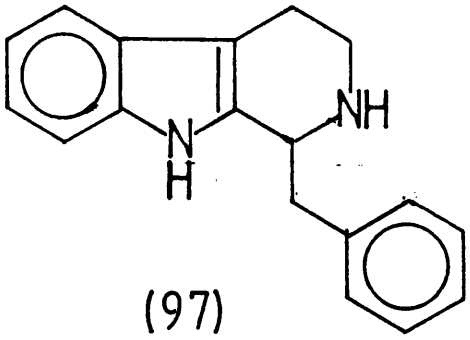
The only carbolines which occur in animal tissues are derivatives of the β-carboline ring system. Evidence has been found for the presence of I-methyl-6-methoxy- (54), I-benzyl-6-methoxy- (96) and I-benzyl-I,2,3,4-terahydro-β-carboline(97), along with a number of other carbolines, in mammalian pineal tissue.[100,101,102] More recent work on the irradiation of brain tissue using an ultra-violet laser microfluorometer[103,104] has revealed the presence of large amounts of β-carbolines.

Work on the biosynthetic origin of these β-carbolines has concentrated on proving that they are derived from the 5-hydroxytryptamine (5-HT) (98) and melatonin (99) with which they occur.[100,101] The treatment of tryptamine (83) and 5-methoxytryptamine (100) with labeled 5-methyl-tetrahydrofolic acid (101) led to the production of I,2,3,4-tetrahydro- (102) and I-methyl-6-methoxy-I,2,3,4-tetrahydro-β-carboline (54).[104,105,106]



(96)

(54)



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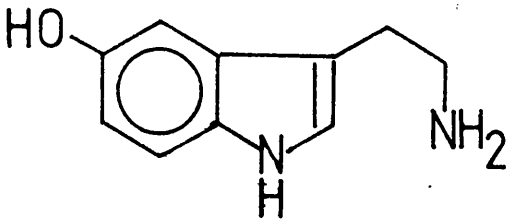

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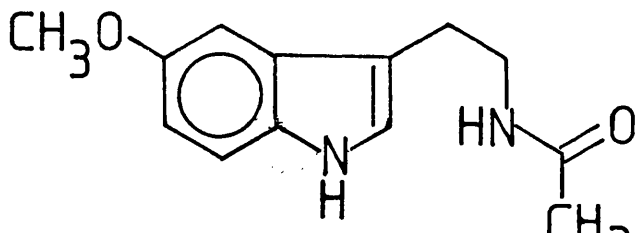

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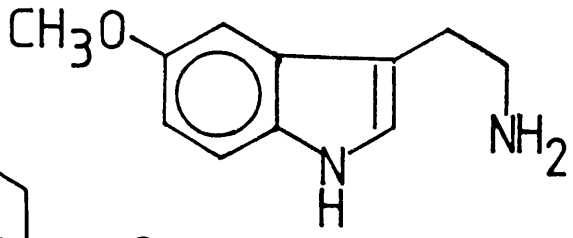

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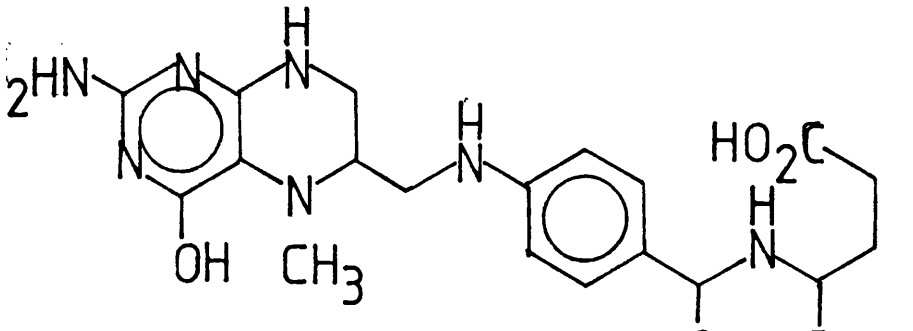
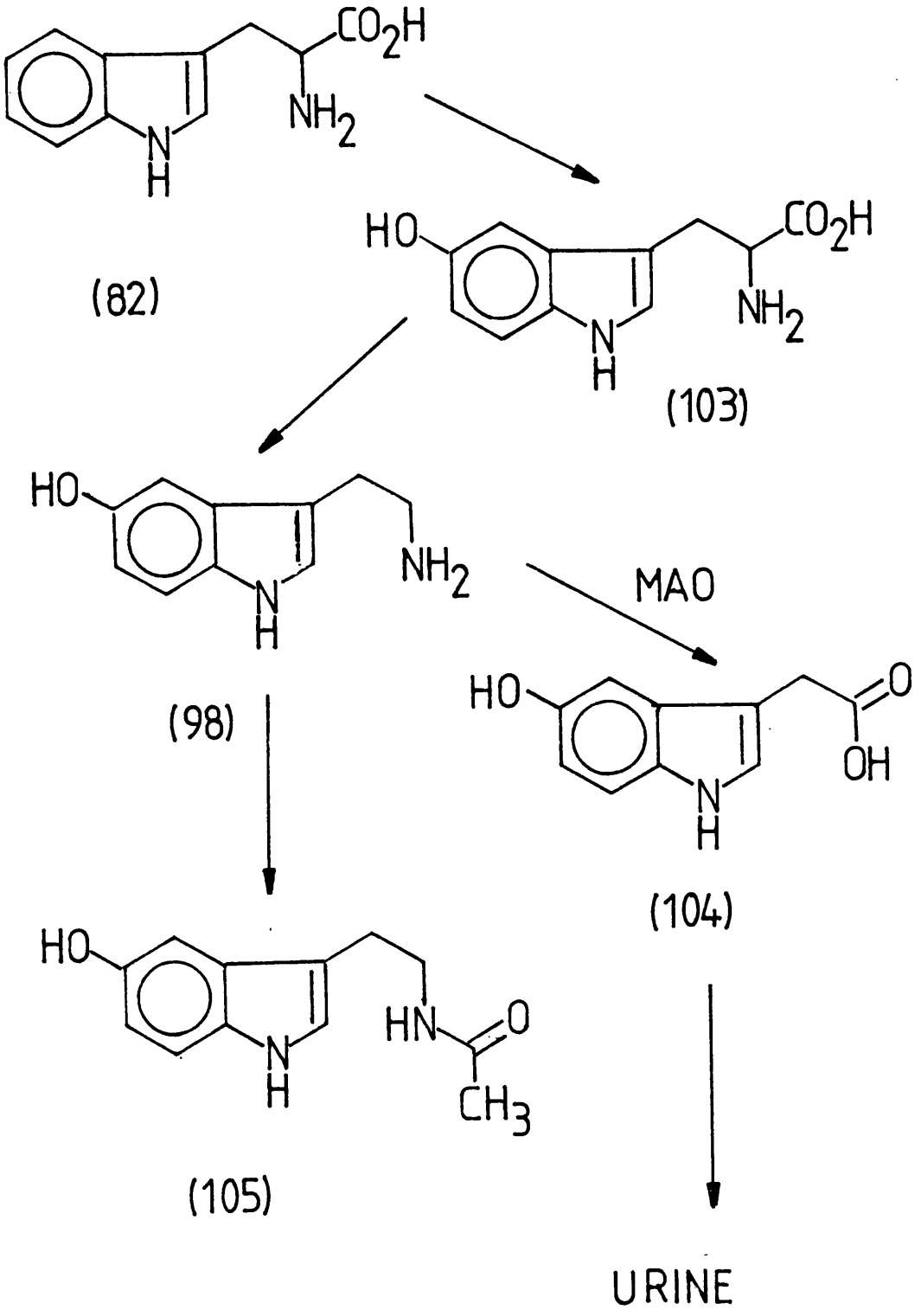


(101)

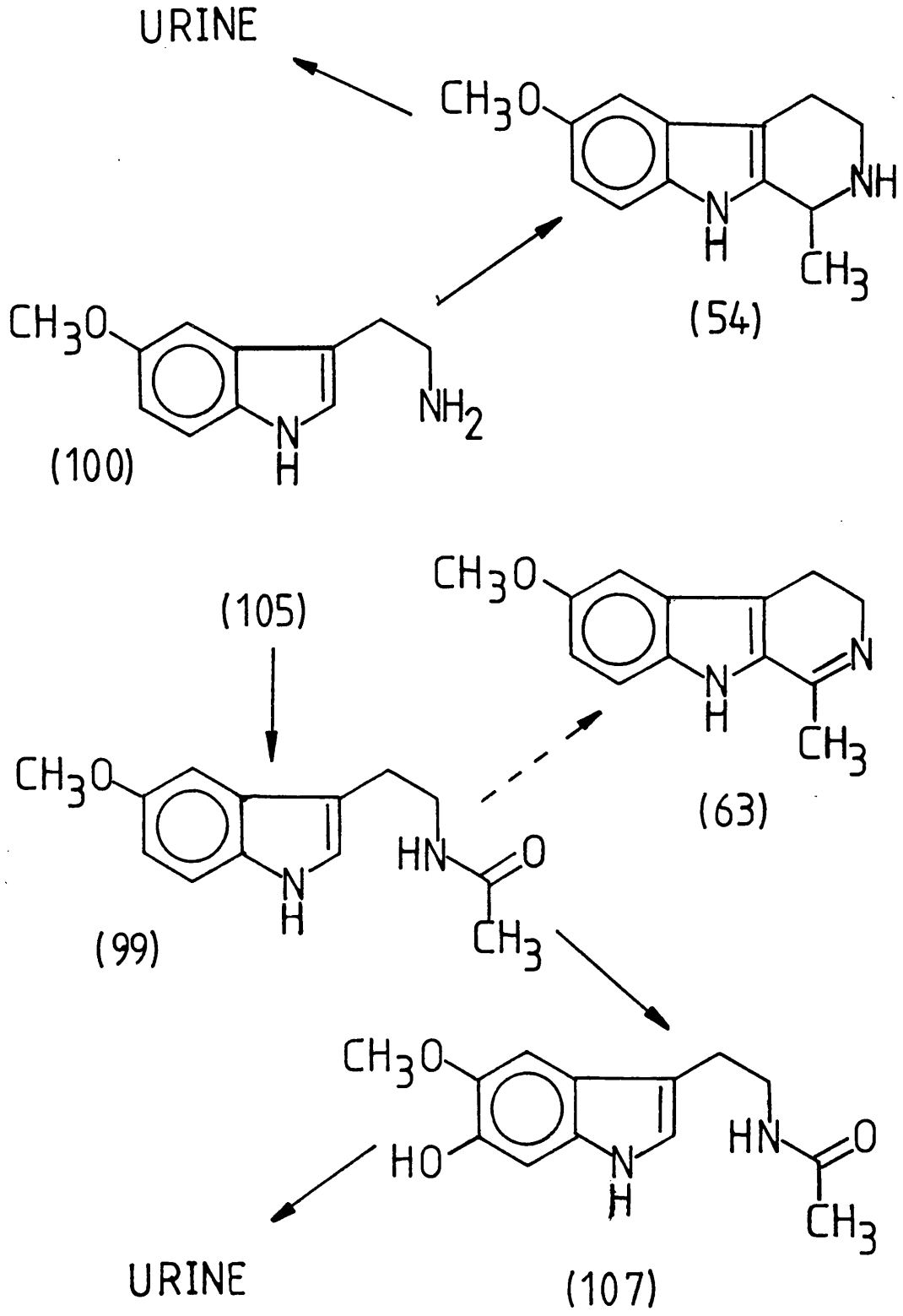
An outline of mammalian β-carboline biosynthesis is given in Scheme 3.[107] 5-HT (98) is formed from tryptophan (82) via 5-hydroxytryptophan (5-HTP) (103)[108] and is converted either to 5-hyroxyindole acetic acid (5-HIAA) (104) and other urinary metabolites by the enzyme monoamine oxidase (MAO), or via N-acetylserotonin (105) to melatonin (99).[111] Melatonin itself can be metabolised via 5-methoxytryptamine (100) or 6-hydroxymelatonin (107) or can be converted into 1-methyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (54). The conversion of melatonin to 6-methoxyharmalan (63) has been found to occur *in vitro* but not definitely *in vivo*.[110]

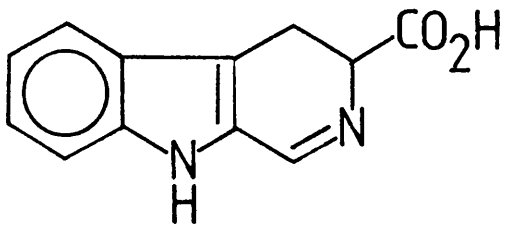
The only other major occurrence of β-carbolines reported in the literature is the isolation of several derivatives from fluorescent human lens proteins;[111] the compounds isolated being 3,4-dihydro-β-carboline-3-carboxylic acid (108) and 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid (109). The formation of these compounds seems to be dependent on age and could be regarded as the products of protein degredation although the authors suggest that 1,2,3,4-terahydro-β-carboline-1,3-dicarboxylic acid (110) is the natural precursor to these compounds.

Scheme 3.


CO2H
NH2
N
H
(82)
HO
CO2H
NH2
N
H
(103)
HO
NH2
N
H
(98)
MAO
HO
O
OH
N
H
(104)
HO
HN
O
CH3
N
H
(105)
URINE

Scheme 3 cont.





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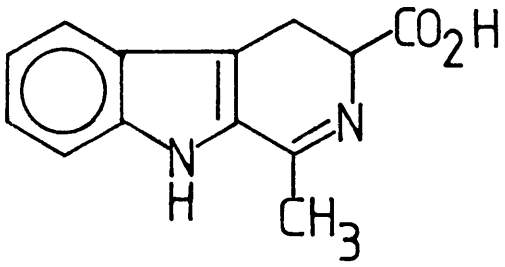

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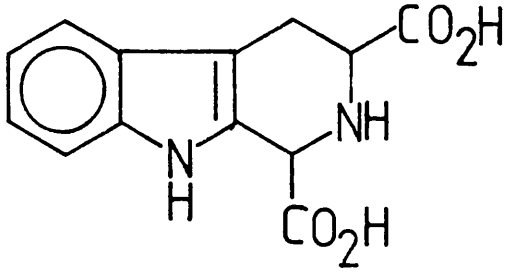
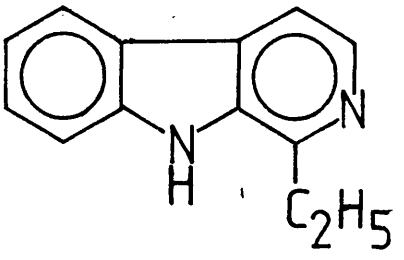


(110)

Pharmacology of Simple Carbolines and its Relationship to Migraine.

Carboline derivatives exhibit a wide range of pharmacological activity.[II2] A large number of β-carbolines, such as I-ethyl-β-carboline (III), are central nervous system depressents[II3,II4] and harmaline (62) and other carbolines inhibit sodium ion transport which leads to a whole range of clinical manifestations.[II5] Various plant extracts, which have been used to treat eye diseases and certain intestinal malfunctions, have been shown to contain a range of β-carboline derivatives which exhibit anticholineesterase activity.[43]

Quaternary salts of I,2,3,4-tetrahydro-β- and γ-carbolines, such as the chlorides (II2) and (II3), show curare like activity[II6] and several β-carbolines, for example the N-aryl derivative (II4), show anti-inflammatory properties.[II7] A large number of β- and γ-carbolines exhibit analgesic and antidepressent activity,[II8,II9,I20] harman (I5) and norharman (7) have been shown to effect the mutagenicity of various anilines and aryl hydrocarbons[I2I,I22] and noreleagnine (53) offers some possibilities in the treatment of alcoholism.[I23]



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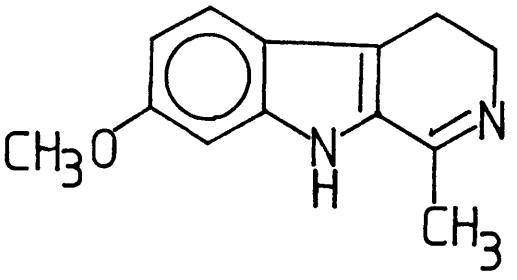

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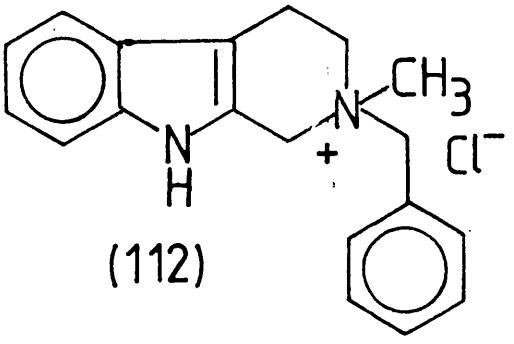

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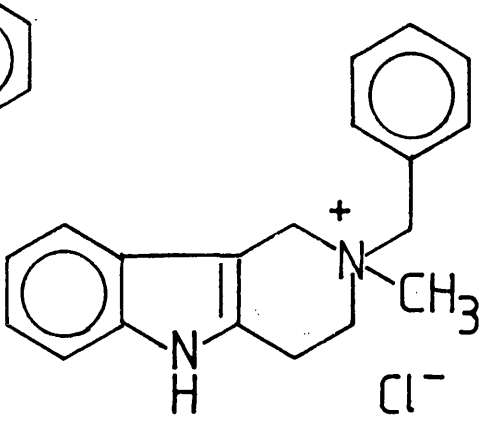

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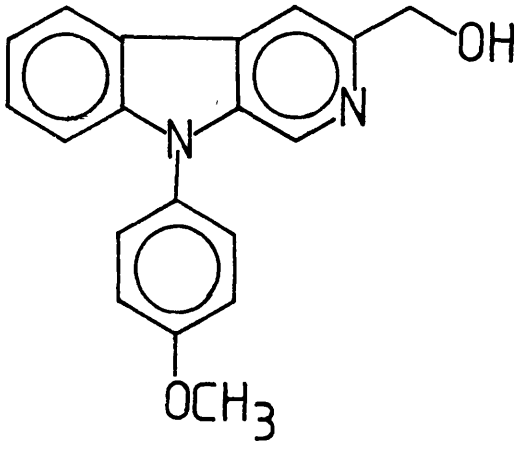

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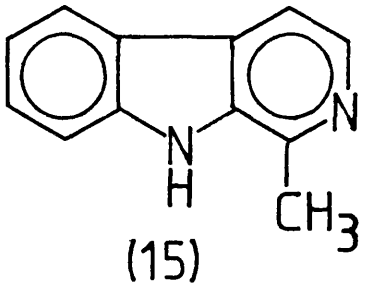

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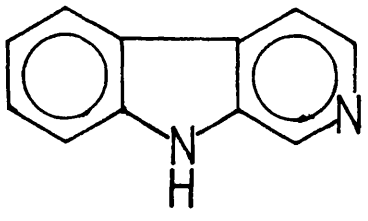

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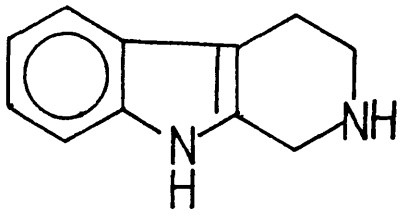


(53)

As previously mentioned the biological rationale for the project described in this thesis, is the synthesis and testing of β-carboline derivatives as agents to combat migraine. It would therefore be useful at this point to outline some facts concerning migraine.

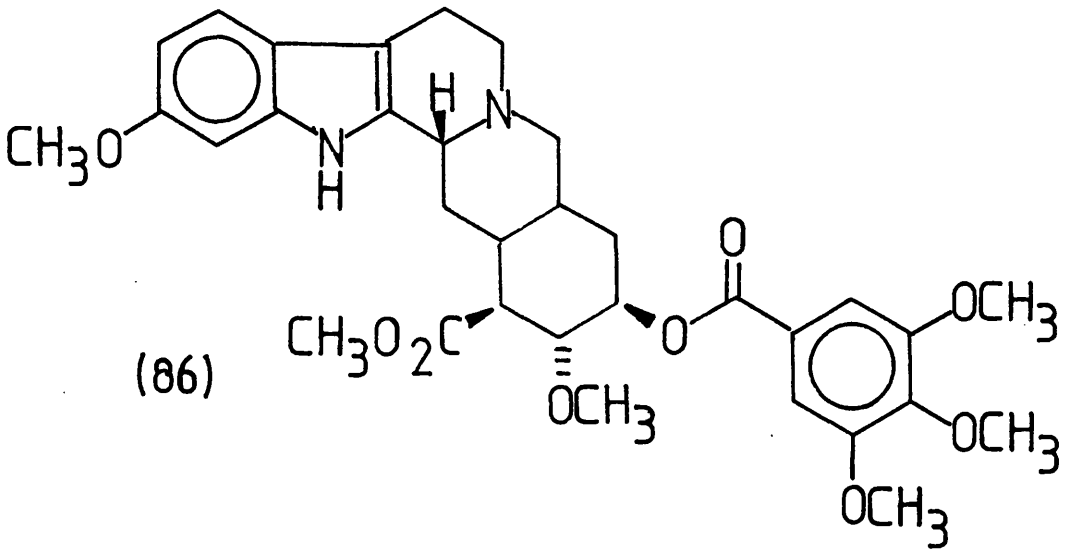
Any discussion of migraine must begin with a statement that the cause of this illness is as yet unknown. Also, a review of the literature regarding its manifestations and causes will indicate that it is most probably a large number of factors, rather than any single one, which are the cause of the attack.

A classical migraine attack is characterised by a sequence of clinical manifestations which have been correlated with alterations in blood vessel size in the brain and scalp.[124] This consists of a marked vaso-constriction in the initial period of the attack followed by dilation in the "headache phase": in fact over-distention of these vessels occurs. It must be emphasised that the alteration in the blood vessel size is regional, affecting a limited segment of the circulation in the head, and hence any investigation into the mechanism of migraine must take this factor into consideration.

These observations suggest that physiologically occurring vasoactive substances may be significantly related to the pathalogical changes in migraine. This does not imply that there is a "headache substance"

responsible for the entire range of migraine symptoms in all patients but merely that the metabolism of vasoactive substances or their action on receptor sites may be involved in some of the symptoms in some patients.

The exact nature of the vasoactive substance involved in migraine attacks has been the subject of considerable research. Some patients have shown increased urinary levels of 5-hydroxyindoleacetic acid (5-HIAA) prior to an attack,[I24] and as 5-HIAA is the major metabolite of 5-hydroxytryptamine (5-HT) it is possible that migraine attacks are caused by a decrease in the blood levels of 5-HT. However such changes in the concentrations of urinary metabolites, which only occur in a small number of patients, are not really a very good indication of the changes occurring in the blood stream. As previously suggested, vascular changes in migraine occur in restricted areas and such a regional change in 5-HT levels would hardly be expected to show up in changes in urinary 5-HIAA levels. Decreases in plasma 5-HT levels have been observed in some patients[I25] prior to migraine attacks , and administration of reserpine (86) which is known to decrease 5-HT levels precipitated an attack. These facts suggest that an endogenous 5-HT releasing factor is present during migraine headaches, and suggest that the drop in plasma 5-HT plays a part in the mechanism of migraine; a view that is supported by the



(86)

evidence that vomitting, which releases 5-HT from the gut, often relieves the symptoms of migraine.

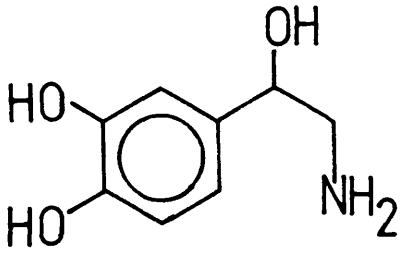
These sudden and drastic changes in 5-HT levels are probably due to some alteration in the sensitivity of receptor sites so that they are hyper-reactive to normal or even minimal changes in 5-HT levels; any increases causing an excessive metabolism of 5-HT and leading to a depletion of the amine. It is therefore necessary that any substance used to treat migraine must in some way effect the metabolism or action of 5-HT. This might be achieved by preventing its metabolism by inhibition of the enzyme involved (monoamine oxidase - MAO), by antagonising its action on receptor sites or by mimicking its action on receptor sites and controling the levels

of 5-HT by a feedback mechanism. However, direct administration of 5-HT to isolated cerebral vessels can produce either a constriction (ie. an effective increase in blood pressure) or a dilation, depending on the region of origin, the species or the tone of the blood vessel,[I26] indicating that there are two types of receptor present. Compounds used to treat migraine should ideally affect only one receptor enabling the drug to alleviate the symptoms of migraine without affecting the action of 5-HT in other parts of the body.

The monoamine oxidase inhibiting potency of a compound and its 5-HT antagonising potency appear to parallel each other[II0] indicating a close relationship between the 5-Ht receptor site and the active site of the metabolic enzyme. Therefore an investigation into the MAO inhibiting properties of β-carbolines could indicate the compounds most applicable to the treatment of migraine.

Monoamine oxidase is one of the oldest classes of enzymes known and it is the enzyme with the largest number and widest variation of inhibitors.[I27] It is through work on MAO that the biochemical, pharmacological and psychopharmacological role of neurohormones, such as 5-HT (serotonin), norepinephrine (II6) and dopamine (II7) have been defined.

Harmaline (62) and related β-carbolines have been shown to be potent MAO inhibitors,[I28] their effect being



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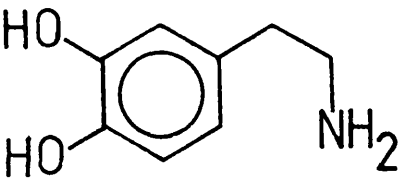

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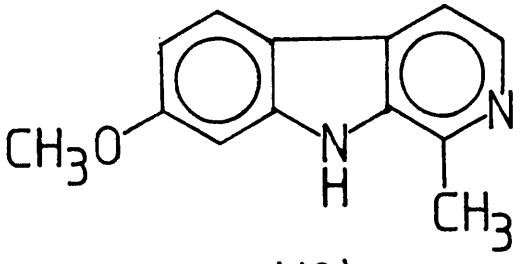

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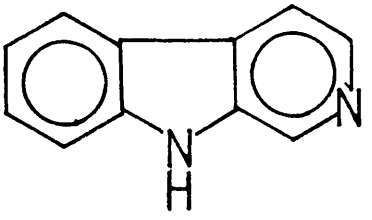

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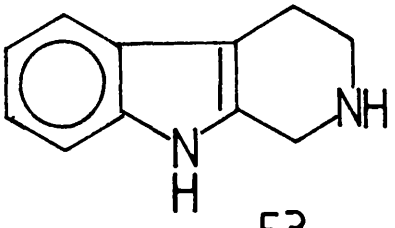

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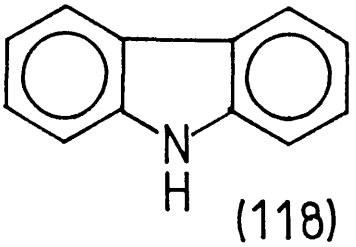


(118)

reversible *in vitro* and faster acting *in vivo*. The degree of saturation of the pyridine moiety of the β-carboline molecule increases their inhibiting effect in the order tetrahydro-, 3,4-dihydro-, fully aromatic β-carboline.[I29] The active site of MAO appears to be filled by the β-carboline since a methyl substituent on various positions, such as C-I and C-8 of (7) and C-I, C-2, C-3 and C-6 of (53), results in a decrease in inhibitory activity.[I30,I3I] Other substituents such as halogens, methoxyl and hydroxyl also reduced inhibition by varying degrees.

An exceptionally high increase in inhibitory activity of the tetrahydro-β-carboline occurred with the introduction of a methyl group onto the indolic nitrogen atom.[I30] A similar effect occurs in the fully aromatic β-carbolines and it is postulated that the electron-donating property of the methyl group either increases the binding capacity of the indole nucleus by the formation of a charge-transfer complex with the enzyme, or binds hydrophobically to the enzyme, or both.[I3I] That the increase in inhibitory activity of the 9-methyl group is at least partly due to the increased electron density is further demonstrated in the aromatic series by a loss in inhibitory activity whan a electron-withdrawing group, acetyl (CH_3CO), is introduced in place of the methyl.[I32]

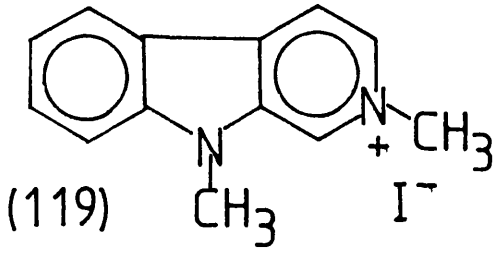
It therefore appears that the binding of β-carboline involves the complexing of the indole alone, or the indole plus the pyridine moiety of the inhibitor, with the enzyme through a possible charge-transfer interaction. The presence of the pyridine nitrogen is essential for the inhibiting effect, since carbazole (II8) is devoid of MAO inhibitory activity.[I29]

Fully aromatic β-carbolines are therefore the most potent MAO inhibitors and as the action of these compounds is restricted to the peripheral organs, their combination of low lipid solubility and high pKa preventing them from entering the brain,[I33,I34,I35] they may be very useful in the treatment of migraine. Some work has been carried out on the inhibitory potency of β-carbolinium salts,[I27,I35,I36] for example 2,9-dimethyl-β-carbolinium iodide (II9) was shown to be more active <u>in vitro</u> than pargyline (I20), itself a potent MAO inhibitor, in arresting tyramine (I2I) oxidation in rat liver, rat heart and human heart preparations. However, because of the difficulty in synthesising derivatives of this oxidation state, particularly derivatives carrying substituents in the pyridine ring at positions other than C-I or N-2, the majority of the work has been carried out on the terahydro- derivatives. Thus a chemical route which would provide derivatives carrying substituents in the C-4 position of the pyridine ring would provide a

wide source of potential MAO inhibitors.

Very little work has been carried out on the 5-HT antagonising properties of carbolines save that some β-carbolines have shown a degree of activity.[139] Studies on 6-methoxy-I,2,3,4-terahydro-β-carboline (I22) have shown that it seems to exhibit a combined mimetic - antagonistic effect in increasing plasma levels of 5-HT by inhibiting the uptake by blood platelets and promoting its synthesis by enzyme activation.[140]

The above data show that β-carbolines have a definite involvement in the pharmacology of 5-HT and that they could possibly have a role in the treatment of migraine.



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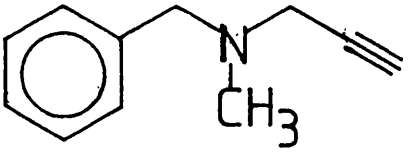

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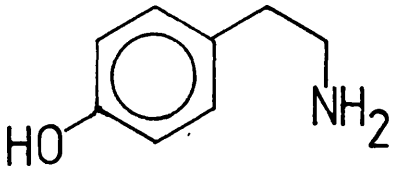

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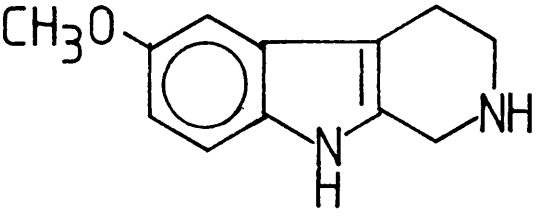

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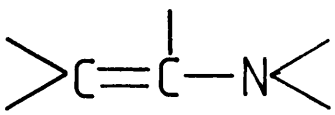
In conclusion it can be stated that the most intersting carbolines, from a biological point of view, are β-carbolines, the fully aromatic members of the series possessing considerable activity against MAO and 5-HT. However, these aromatic carbolines are not easily prepared, especially compounds substituted in the pyridine ring, and synthetic procedures which provide a facile route to aromatic β-carbolines and their salts would generate a large supply of compounds for biochemical evaluation.

The objective of the work reported in this thesis was to produce a general method for the preparation of 4-substituted fully aromatic β-carbolines and to study their chemistry and biology.

DISCUSSION

As mentioned briefly in the introduction, the primary chemical aim of the research reported in this thesis was the investigation of the enamine character of dihydrocarbolines. In particular the idea was to reproduce the enamine reactions of dihydroisoquinolines, especially I,2-dihydroisoquinolines, in the carboline series.

The α,β-unsaturated amine system (I23), named enamine to emphasise its similarity to an enol (I24), has been known since I9I6[I4I] but the synthetic potential of such compounds was only realised in the early nineteen-sixties[I42] and has been extensively investigated since that time.[I43] The enamine function may be regarded as a resonance hybrid of the canonical forms (I23) and (I25), so that electrophilic reagents are expected to attack at either the nitrogen atom or at the β-carbon atom. In the derived iminium ion (I25), nucleophilic reagents attack at the α-carbon atom.



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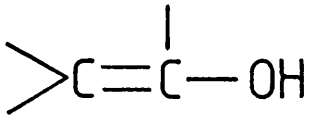

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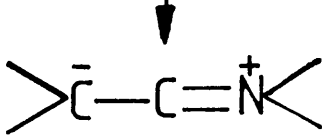

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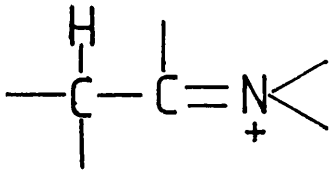


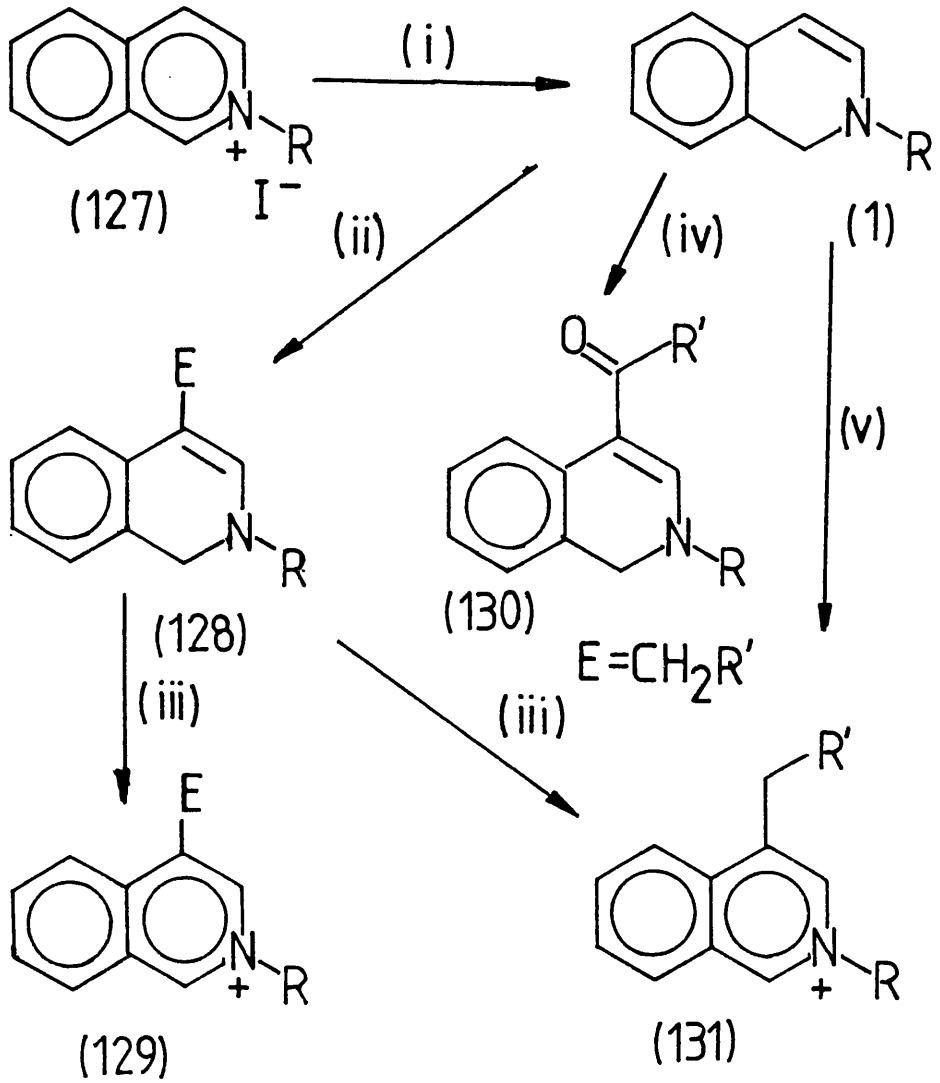
(126)

It was noted by Battersby et al.[I44,I45] that I,2-dihydroisoquinolines (I) exhibit enamine character, and are susceptible to electrophilic attack at C-4. The system is generated by reduction of a quaternary isoquinolinium salt (e.g.(I27)) and the general course of the reaction is outlined in Scheme 4 in which some of the more important reactions are summarised.

2-Alkyl-I,2-isoquinolines (I) react with a variety of activated halides to yield isoquinolinium salts (I29, E = alkyl or benzyl) after oxidation of the intermediate 4-alkyl or 4-benzyl-I,2-dihydroisoquinolines (I28, E = alkyl or benzyl) with iodine.[I46] The yields of products are not outstanding but compare favourably with those from the more traditional isoquinoline syntheses.[I]

I,2-Dihydroisoquinolines (I) have also been reacted with a variety of acid chlorides to yield the expected vinylogous amides (I30) in the majority of cases.[I47,I48] The acylation proceeds most readily with aromatic acid chlorides apart from some unaccountable exceptions such as cinnamoyl chloride. Of the heterocyclic acid chlorides tried only 2-furoyl chloride was observed to react.[I47] Simple aliphatic acid chlorides and compounds such as pyruvic acid chloride and ethyl chloroformate failed to yield the expected products, but substituted acid chlorides such as chloroacetyl chloride gave the expected product. It should be stated that in all such reactions complex

Scheme 4.



R = H, alkyl

E = alkyl, aryl, acyl

(i) $LiAlH_4$

(ii) R'-Hal, Ar-Hal or R'CHO

(iii) I_2

(iv) R'COCl

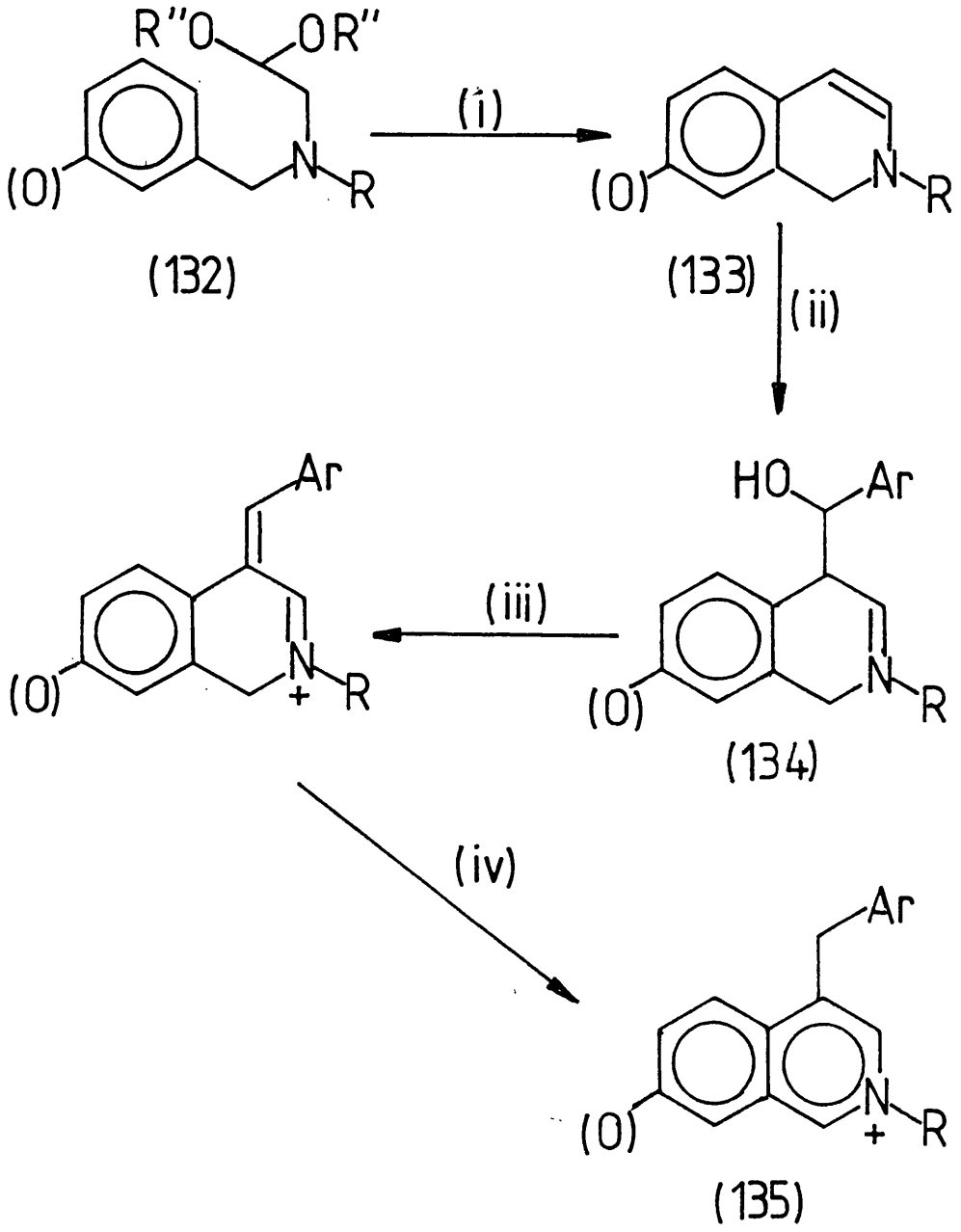
(v) R'CHO

mixtures form from which the 4-acylated products are isolated by chromatography, thus failure to isolate the required compound does not imply a lack of reaction.

The reaction of I,2-dihydroisoquinolines with aromatic aldehydes in acid solution gives the isoquinolinium salts (I3I, R' = Aryl)[I49] and this has proven to be a very important process. Thus Bobbitt *et al.* have reported[I50] that when benzylaminoacetaldehyde dialkylacetals (I32) are heated under reflux with concentrated hydrochloric acid in ethanol in the presence of an aromatic aldehyde, good yields of the 4-benzylisoquinoline derivatives (I35) are obtained. The reaction proceeds via the I,2-dihydroisoquinoline (I33) and the mechanism for the reaction is summarised in Scheme 5.[I5I] The intermediate 4-benzylidene-I,4-dihydroisoquinolines (I34) have been isolated in several cases.[I49]

In extending the enamine reactions outlined above to the carboline ring system, it was decided at the outset to prepare relatively simple derivatives of β-carboline ie. (I36), (I37) and (I38). Only later did we decide to concentrate mainly on compounds of the last two types which necessitated the development of simple and reliable syntheses of the key intermediates (I39, R = removable protecting group) and (I40).

Scheme 5.

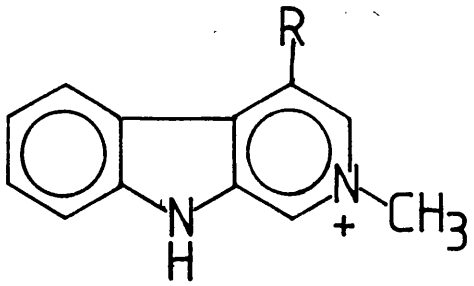


(i) H^+, heat

(ii) ArCHO

(iii) - H_2O

(iv) H^+



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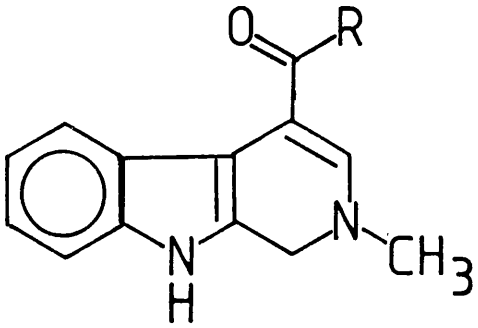

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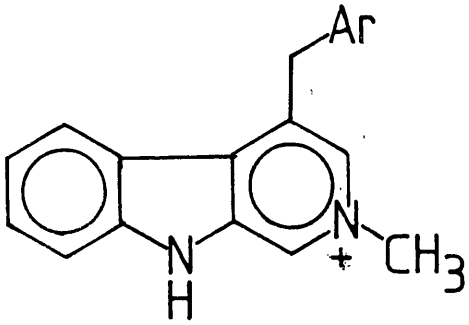

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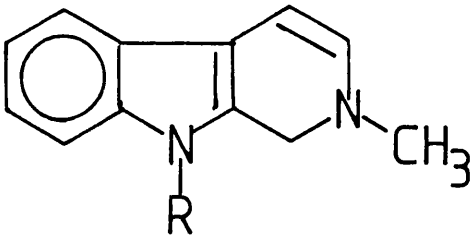

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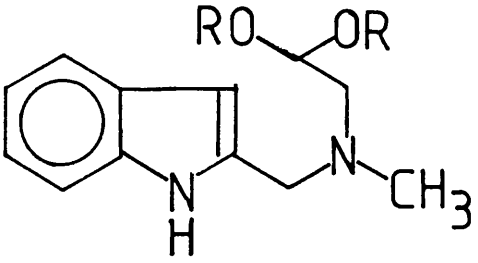


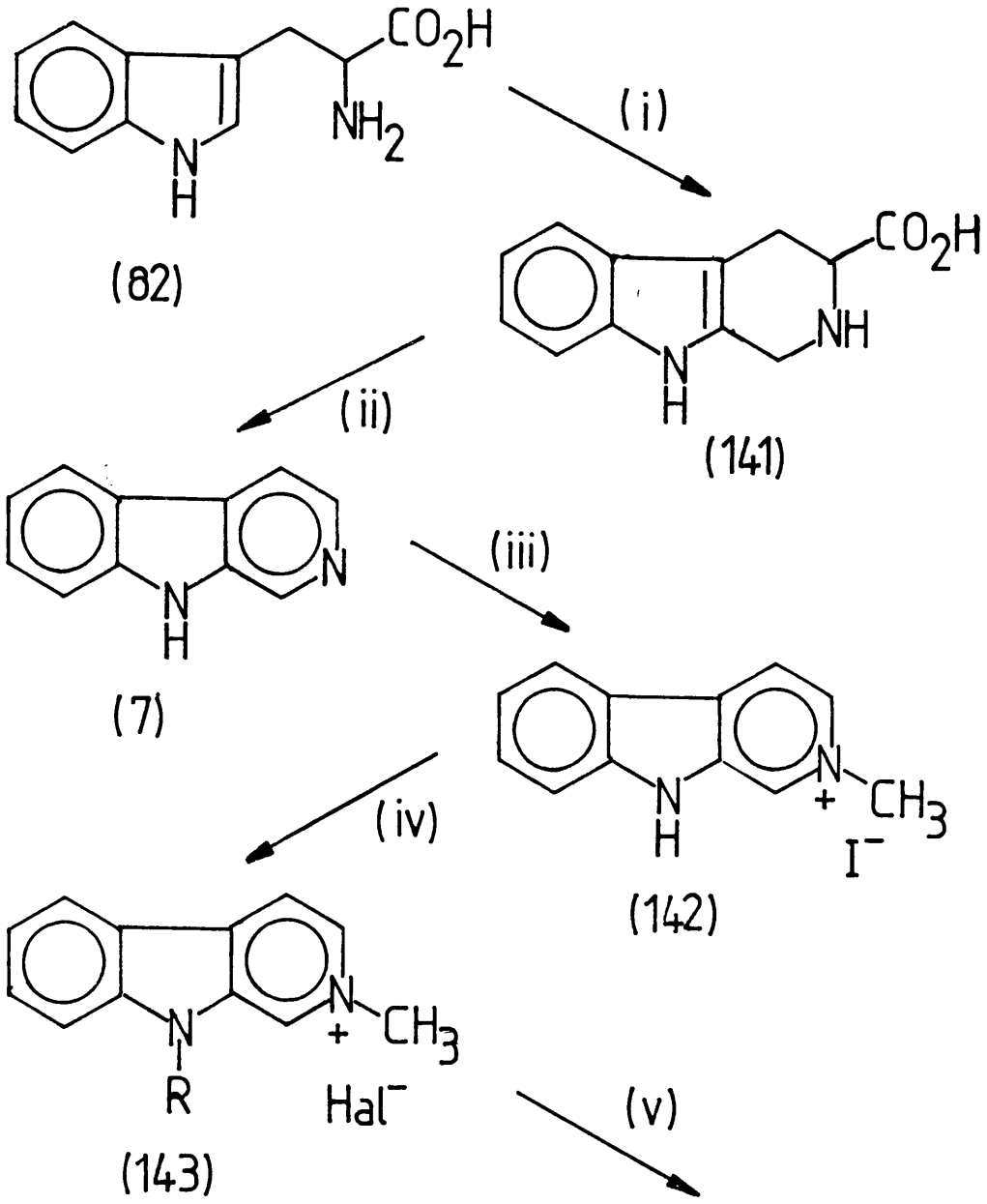
(140)

In this account the synthetic procedures based on the I,2-dihydro-β-carboline system (I39) will be reported before those based on the indoleamino-acetal intermediate (I40), although in practice the work was carried out virtually concurrently.

The proposed sequence involving the intermediate (I39) is outlined in Scheme 6. There are a wide and varied range of "one off" syntheses for the fully aromatic carbolines, such as (7), all of which are of little or no versatility and will not be discussed further. Other "classical" syntheses of heterocycles, such as the Pschorr-type ring closure and the Waterman and Vivian carbazole synthesis (nitrene intermediates),[I52] give poor yields and mixtures of products. They are also of little versatility.

Application of the Graebe-Ullman carbazole synthesis to the carboline ring system has been more successful.[5,I53] Thus heating the triazole (I47) with fused zinc chloride, syrupy phosphoric acid or polyphosphoric acid gives the required β-carboline in variable yields.[I54] In this reaction cyclisation may also take place at the pyridine α-position and for this reason the reaction gives much better yields when 2- and 4-substituted pyridyltriazoles are used en route to form α- and especially δ-carbolines respectively.[I55-I58]

Scheme 6.



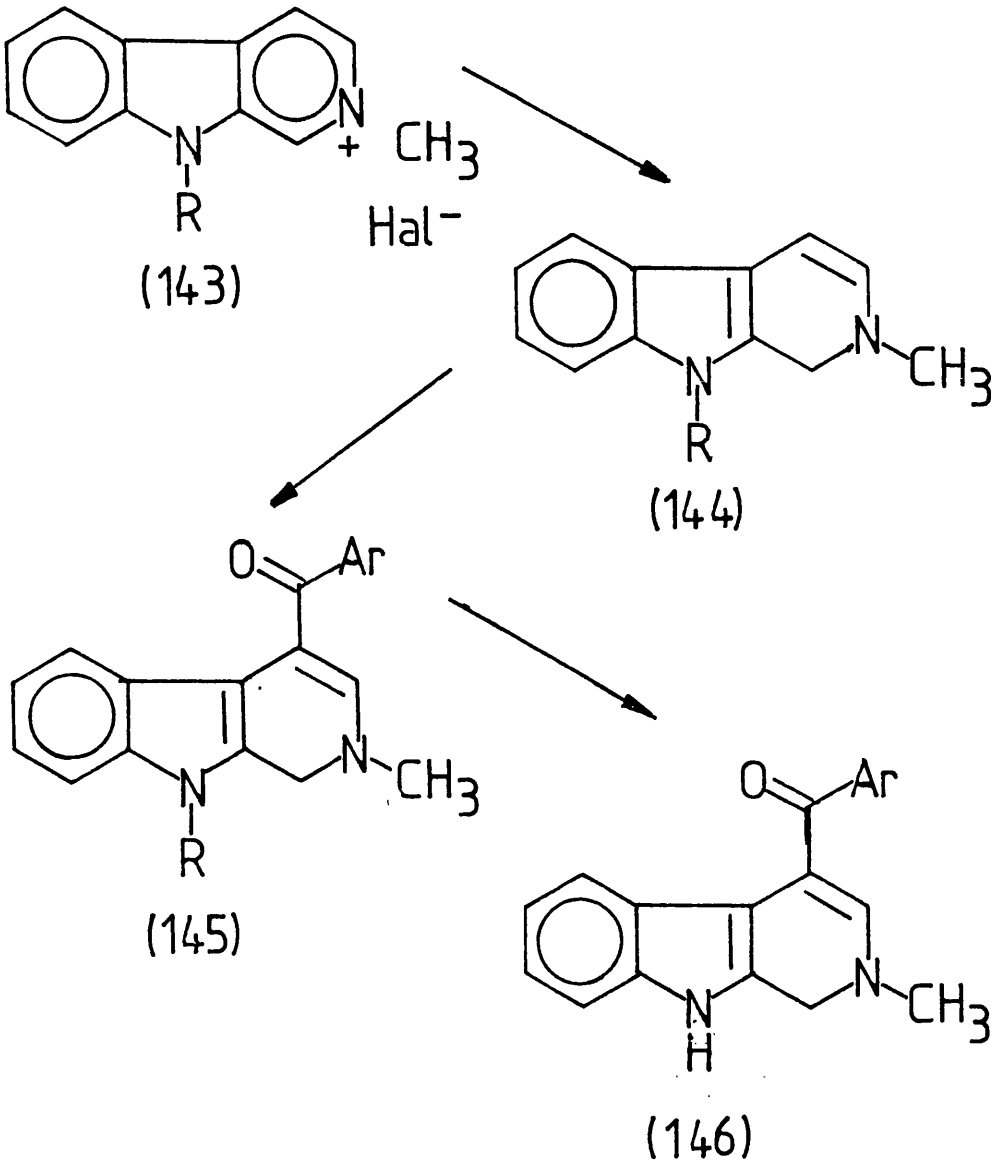
(i) HCHO

(ii) Oxidation

(iii) CH_3I, Acetone

(iv) R-Hal, Base

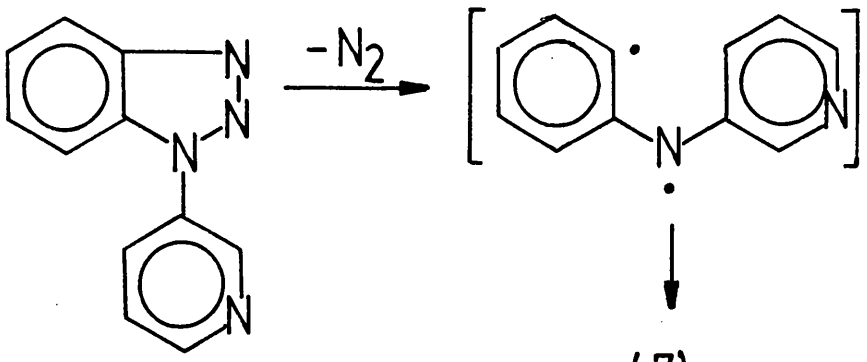
Scheme 6 cont.



(v) Reduction

(vi) ArCOCl

(vii) - R



(147) (7)

Tetrahydro-β-carbolines can be aromatised by a number of oxidising agents, such as lead tetra-acetate or sulphur in xylene, but the reaction is only generally applicable to extended carboline systems and is not usually successful for simple carbolines.[153]

The most reliable method for the synthesis of β-carboline (7) is the oxidative decarboxylation of the readily available I,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (I4I). The method was first used by Kermack et al.[159] but was later improved by Harvey, Miller and Robson.[160] The procedure involves the condensation of tryptophan (82) with formaldehyde in aqueous sodium hydroxide solution, at 35-40°C, to yield the I,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (I4I). This is oxidised with acidic potassium dichromate to β-carboline (7). In a modification developed by Snyder, Walker and Werber[161] the intermediate tetrahydro- acid (I4I) is not isolated but oxidised in situ.

The attraction of this method is its mild conditions, shorter reaction time, simple work up and relatively good yield, 48% overall for the two stages on a 0.001 molar scale.[160,161]

In the authors hands, however, the procedure was less successful, all attempts to effect the reaction in the 15 hour condensation time recommended by Harvey, Miller and Robson[160] yielded almost no tetrahydro- intermediate. An extended reaction time of 48 hours is required which is as reported by Snyder, Walker and Werber.[161] This usually gave a reasonable yield of product (141); typically around 60%.

This was still disappointing, however, compared with the 80% yield reported in the literature.[160] None the less that quoted was for a 0.001 molar scale reaction wheras that of the author was for a 0.05 molar scale reaction, and it was probable that the difference in yield was due to a scale-up effect. A similar procedure used by a group of Russian workers[162] is said to give yields comparable with those in the original literarure[161] but only for milligram scale reactions. It was possible, though, that the lower yield experienced by the author was due to the inherent difficulties in isolating amino acids combined with inexperience in handling this type of reaction. It was decided to try and overcome this difficulty by concentrating on the "one-pot" procedure

of Snyder et al.[161]

Even this procedure turned out to be less than satisfactory. When the literature procedure was repeated on the reported scale of 0.05 mol., it was only possible to obtain the reported yield of β-carboline (7) (34%) through exhaustive extraction of the reaction mixture with ether over two days, wheras the literarure suggested a simple extraction with five lots of ether.[160,161] Scaling up the reaction to a 0.3 molar scale caused the yield of (7) to drop to 14%, even after seven days continuous extraction with ether. Substitution of ether by ethyl acetate, dichloromethane or chloroform led to very little improvement in yield.

The primary cause of this drop in yield appeared to be the large quantities of chromium (II) oxide or hydroxide formed as a by-product in the work up. This grey-green gelatinous mass seemed to trap the β-carboline in some way and prevent its extraction into the organic solvent. This trapping was probably due to the high water content and ionic nature of the inorganic gel preventing the physical penetration of the organic solvent into the gel. Chelation of the chromium by the β-carboline cannot, however, be definately ruled out.

The large quantities of the chromium containing by-products also posed problems of sheer bulk and physical handling and mechanical losses were consequently quite high.

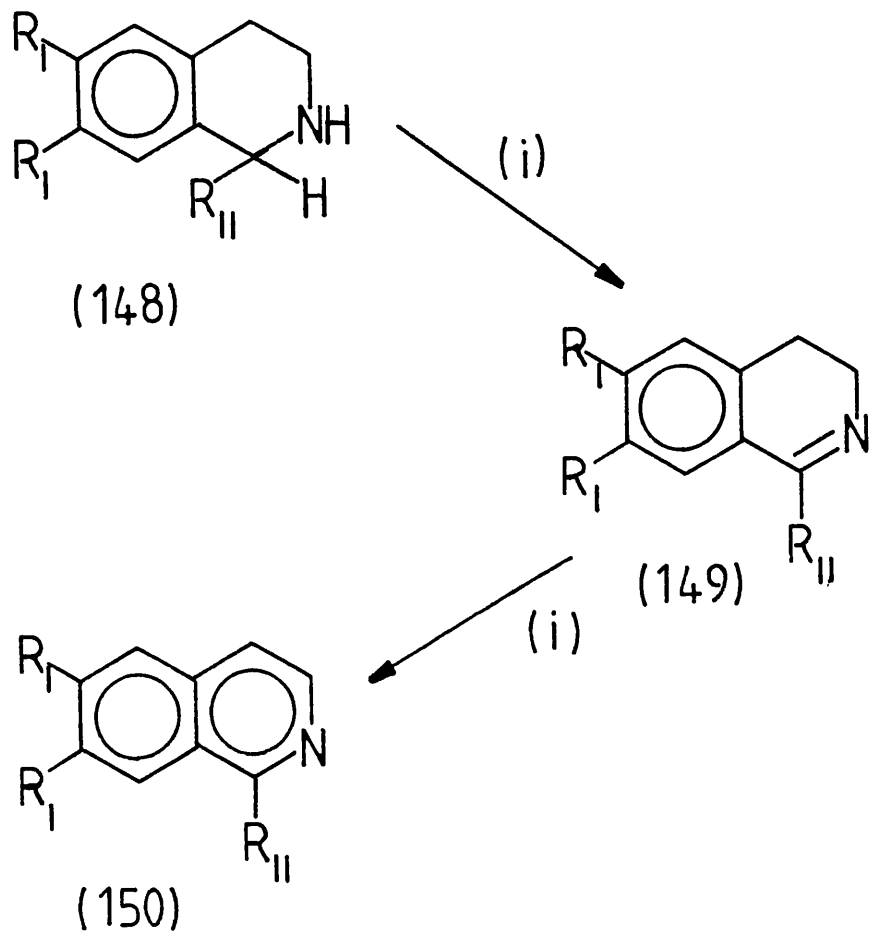
It appeared, then, that in order to avoid having to carry out numerous repetitive small-scale preparations of β-carboline, a modification of the synthetic procedure was necessary, enabling it to be scaled up, so that sufficient β-carboline would be available for subsequent reactions.

A survey of the literature showed that of the other oxidising agents that had been used[153] to carry out the oxidative decarboxylation of (I4I) or related systems, only sodium hypochlorite solution fulfilled the criteria of being readily available, cheap and giving a good yield.[163,164]

In the author's hands the procedure gave reasonable yields even when scaled up, although once again continuous extraction of the aqueous layer was required to obtain a reasonable yield. β-Carboline appears not to be as soluble in organic solvents as the literature seems to imply. There is also the problem of having to isolate the intermediate I,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (I4I) prior to oxidation by the hypochlorite. In terms of overall yield from tryptophan, the synthetic method involving the hypochlorite oxidation showed no real advantage over the method involving the dichromate oxidation.

One other oxidising agent was investigated; potassium nitrosodisufonate ($(KSO_3)_2NO$) or Fremy's Salt.

Scheme 7.



R_I = H, OCH_3

R_2 = H, CH_3

(i) Fremy's Salt

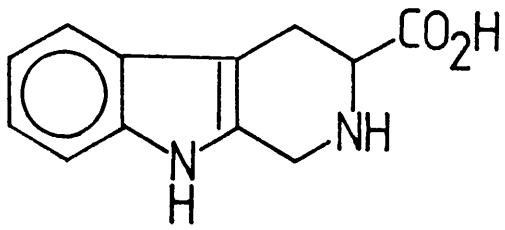
This reagent has been used to oxidise tatrahydroisoquinolines (I48) to the fully aromatic compounds (I50) via the 3,4-dihydroisoquinolines (I49).[165] The yields are variable depending on the substituents (Scheme 7).

Reaction of Fremy's Salt with I,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (I4I) under the literature conditions led to the formation of a red gum, the TLC of which showed many components, none of which was the required β-carboline (7), 3,4-dihydro-β-carboline (I5I) or 3,4-dihydro-β-carboline-3-carboxylic acid (I08). The procedure was therefore abandoned.

It would probably have been more applicable to study the action of Fremy's Salt on I,2,3,4-tetrahydro-β-carboline (53) itself but, as this compound is difficult to prepare, the synthetic route would not have offered a convenient source of β-carboline.

In retrospect the lack of sucess in these reactions probably involves the great sensitivity of the indolic system to oxidants. Thus it might have been useful to have employed less energetic oxidants.

An alternative route to β-carbolines, still starting from tryptophan (82), is based on an adaption of the Bischler-Napieralski synthesis of 3,4-dihydroisoquinolines.[8] The initial stage of the reaction consists of the cyclodehydration of N-formyl-tryptophan (I52) and the mechanism is fundamentally similar to the intermolecular acylation



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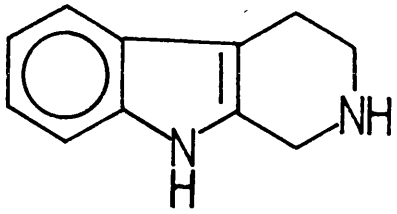
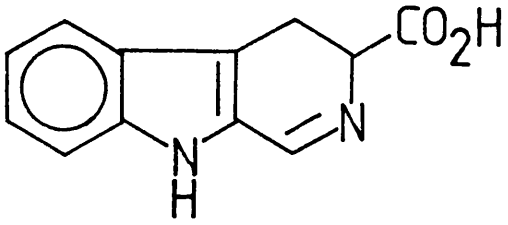
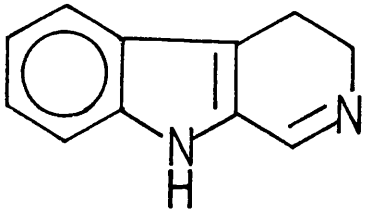


(53)



(108)



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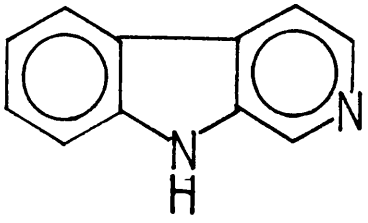


(7)

of indoles by amines in the presence of phorphorus oxychloride - the Vilsmeier Reaction.

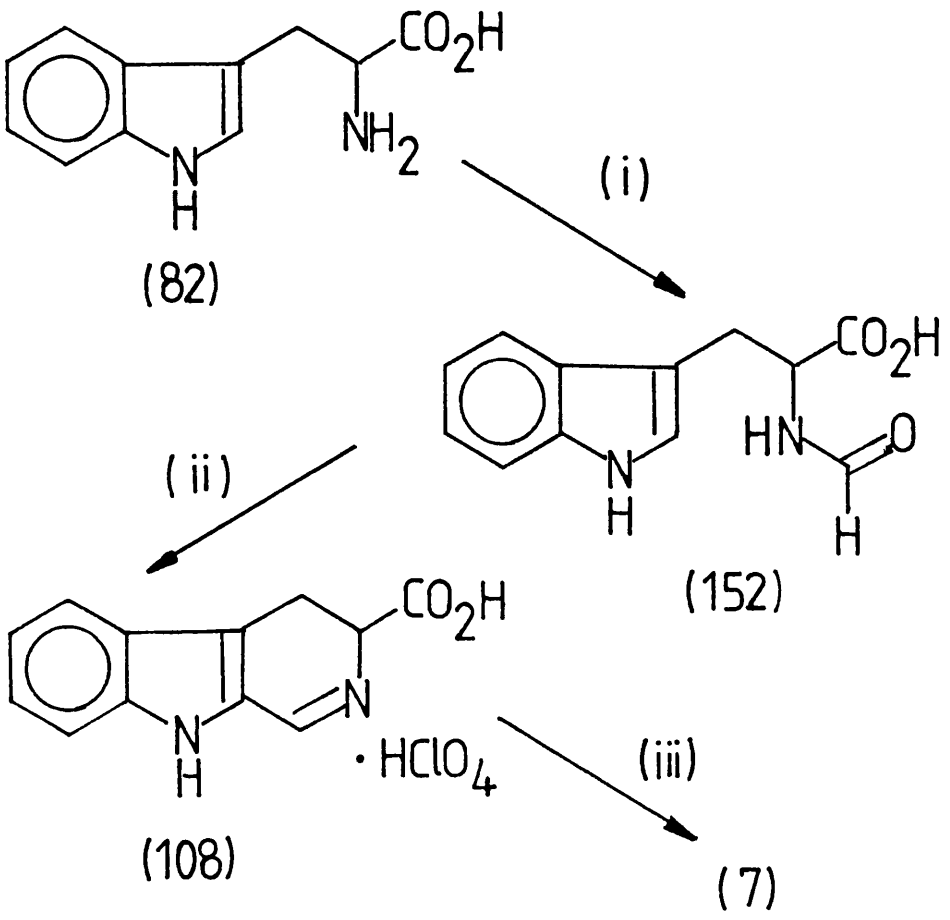
This versatile reaction has been widely applied to the synthesis of 3,4-dihydro-β-carbolines (I5I) from tryptamine (83). The usual reagents used for the reaction are phosphorus pentoxide, phosphorus oxychloride or polyphosphoric acid in the temperature range from ambient to 200°C.[I53,I66,I67] The attempted cyclisation of N-formyl-tryptophan (I52) by means of classical reagents failed to yield the corresponding 3,4-dihydro-β-carboline-3-carboxylic acid.[I60] The use of polyphosphoric acid and phosphorus oxychloride brought about the ring closure of N-formyl-tryptophan but this was invariably accompanied by the loss of carbon dioxide and hydrogen atoms to give β-carboline as the only isolable product in very low yield.[I68,I69]

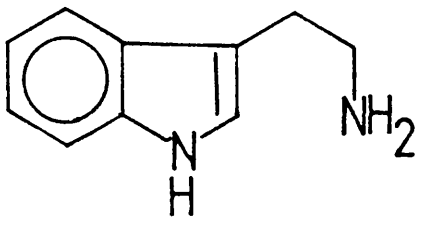
Recently the chloroform soluble phosphate polymer, PPE, has been recommended as an alternative cyclisation catalyst.[I70,I7I] The yields are reported to be generally superior to those for the classical reagents.

It was decided to investigate this route to 3,4-dihydro-β-carboline-3-carboxylic acid (I08) and to see if it could provide a facile route to β-carboline (7).

D,L-Tryptophan was formylated with 98% formic acid and acetic anhydride in a reasonable yield according to a literature procedure.[I72] The N-formyl- compound was

Scheme 8.





(83)

(i) HCHO, $(CH_3CO)_2O$

(ii) PPE, $HClO_4$

(iii) Oxidation

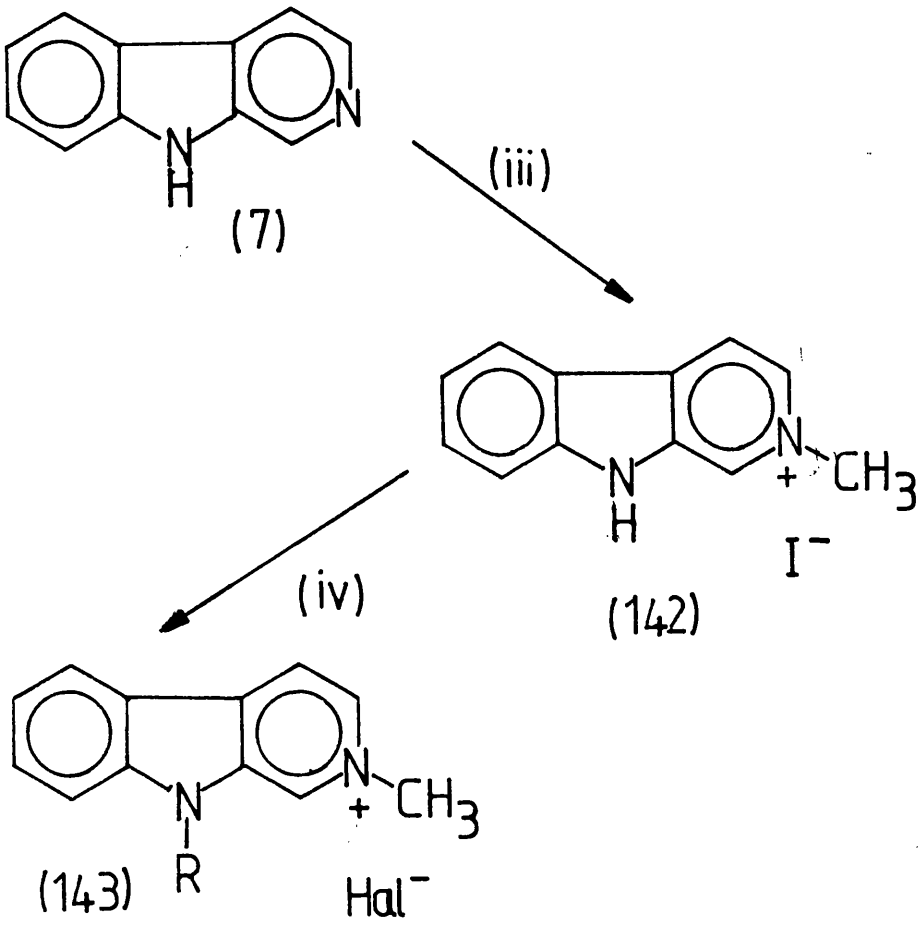
easily cyclised (Scheme 8) with PPE in chloroform solution at room temperature and careful addition of perchloric acid gave (I08) as a crystalline perchlorate salt in 74% yield. The melting point and spectral characteristics corresponded to those in the literature,[I7I] the strongest confirmation being the absorption at λ_{max} 365-7 nm in the ultra-violet spectrum due to the 3,4-dihydro-β-carboline chromophore.[I7I]

According to the literature, to secure a good yield of the perchlorate salt (I08) the reaction media needs to be kept acidic throughout the work up. The salt, fairly stable in a purified state, is unstable in alkaline solution and suffers rapid oxidative change above pH 7. The above observations suggest that careful acidic oxidative decarboxylation or basic hydrolysis might convert (I08) to β-carboline (7).

Oxidation of (I08) with both acidic potassium dichromate and sodium hypochlorite solution at room temperature and at $0^{o}C$ gave black tars which contained only traces of the required β-carboline by TLC. A similar tar was obtained during the synthesis of (I08) if the addition of perchloric acid was not carefully controled.

Basic hydrolysis was attempted by the addition of excess sodium carbonate solution to a vigorously stirred solution of (I08) in water and chloroform, with benzyl triethylammonium hydroxide as phase transfer catalyst.

Scheme 6 (part of).



R = Removable protecting group

(iii) CH_3I, Acetone

(iv) R-Hal, Base

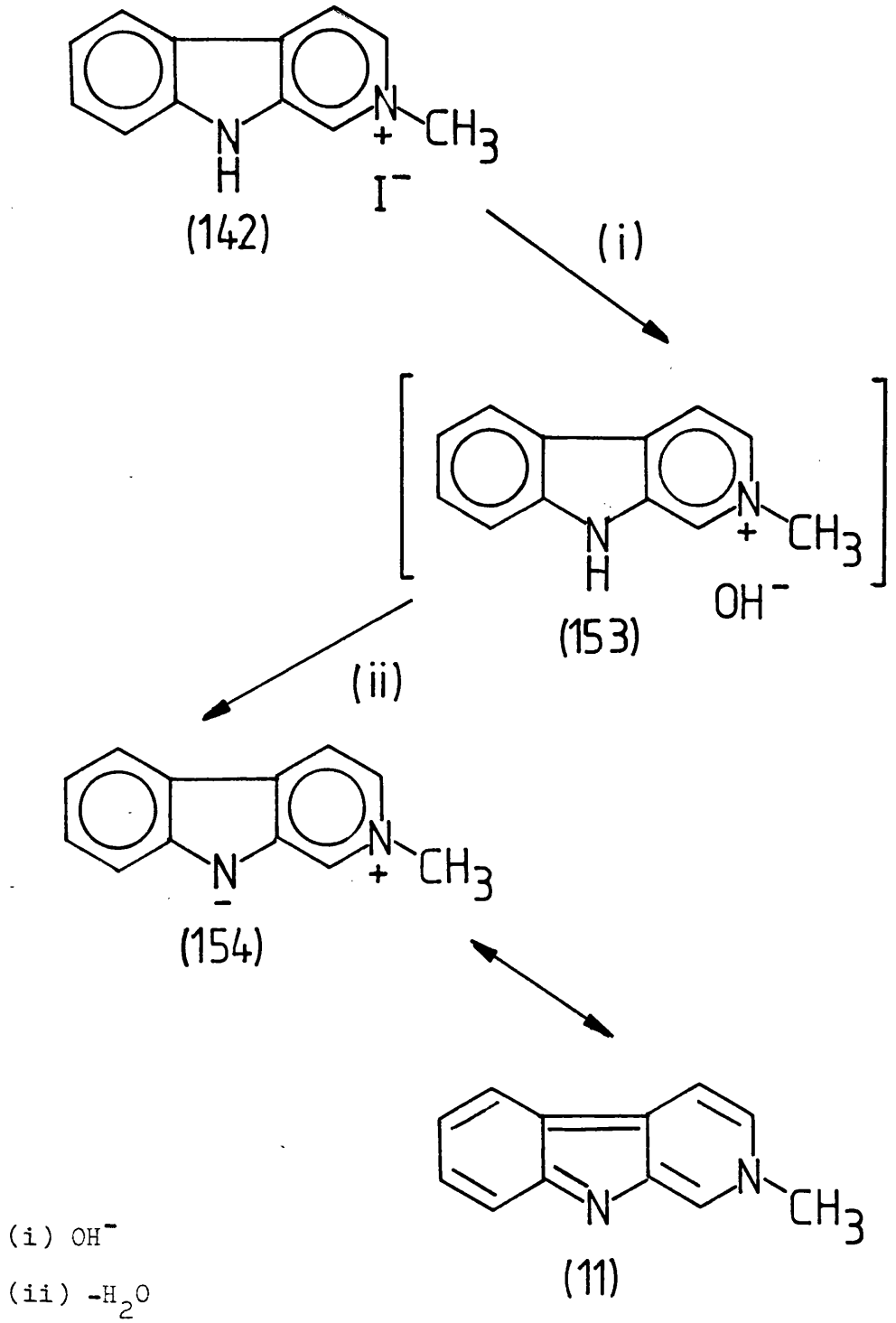
After stirring at room temperature for 24 hours, the chloroform layer contained no β-carboline or salt (I08). Whether the hydrolysis failed or whether the β-carboline remained in the aqueous layer was never ascertained.

It was decided that even with its limitations and need for numerous repetitions, the "one-pot" cyclisation and oxidative decarboxylation of tryptophan[I6I] was the best method for the preparation of β-carboline bearing in mind the need to avoid spending an excessive amount of time on the preparation of starting materials. This led, however, to a constant shortage of precursor for subsequent reactions.

β-Carboline was quaternised (Scheme 6) by reaction with iodomethane following the procedure which has been carried out by many authors.[I73,I74] The quaternary salt was obtained in high yield and the melting point and spectral data corresponded with those in the literature.[I73]

When a 2-alkyl-β-carbolinium salt, unsubstituted at the indole nitrogen (such as (I42)), is treated with strong alkali, a yellow or orange strongly basic solid separates.[I53] Although such products almost invariably give poor microanalytical values[I75] they can be shown to be derived from the quaternary hydroxide (I53) by loss of a molecule of water - hence the name anhydro-bases or anhydronium bases.[I76] Most of the evidence regarding the structure of these bases has been summarised

Scheme 9.



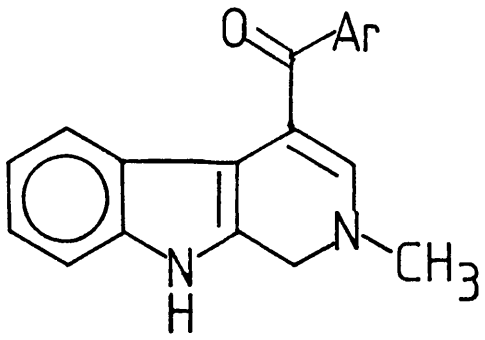
(i) OH^-

(ii) $-H_2O$

and this indicates[167] that they are best described as a resonance hybrid of the structures (II) and (I54). Most of the evidence from spectral and molecular orbital calculations favour a predominance of the covalent form (II) but these compounds react with ionic reagents as if they had the structure (I54), emphasising their zwitterionic character.

As mentioned at the start of this discussion, the aim of the work described in this thesis was the preparation of β-carboline derivatives such as (I37) and (I38) unsubstituted at the indole nitrogen. The ease of removal of the indole proton could have posed a serious problem in the preparation of the I,2-dihydro-intermediate (I44, R = H) if the reducing agents used for the conversion of (I42) to (I44) were sufficiently basic to remove the proton. To guard against this possibility it was decided to substitute the indole nitrogen of (I42) with a removable protecting group.

During their investigations into syntheses using N-protected-2-lithioindoles, Sundberg and Russell compared the properties of various nitrogen protecting groups for indole.[177] Whilst it is very easy to substitute indole on the nitrogen, removal of the substituent is usually extremely difficult. These authors found that the benzesulphonyl group was easily introduced and could be removed by relatively mild alkaline hydrolysis in excellent yields (80-95%).[177,178] They also found that



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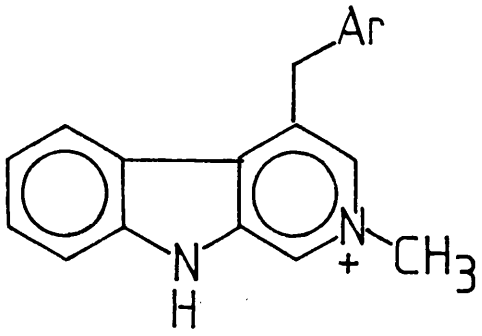

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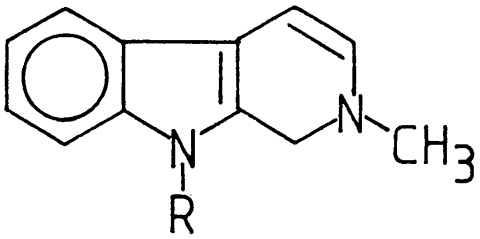


(144)

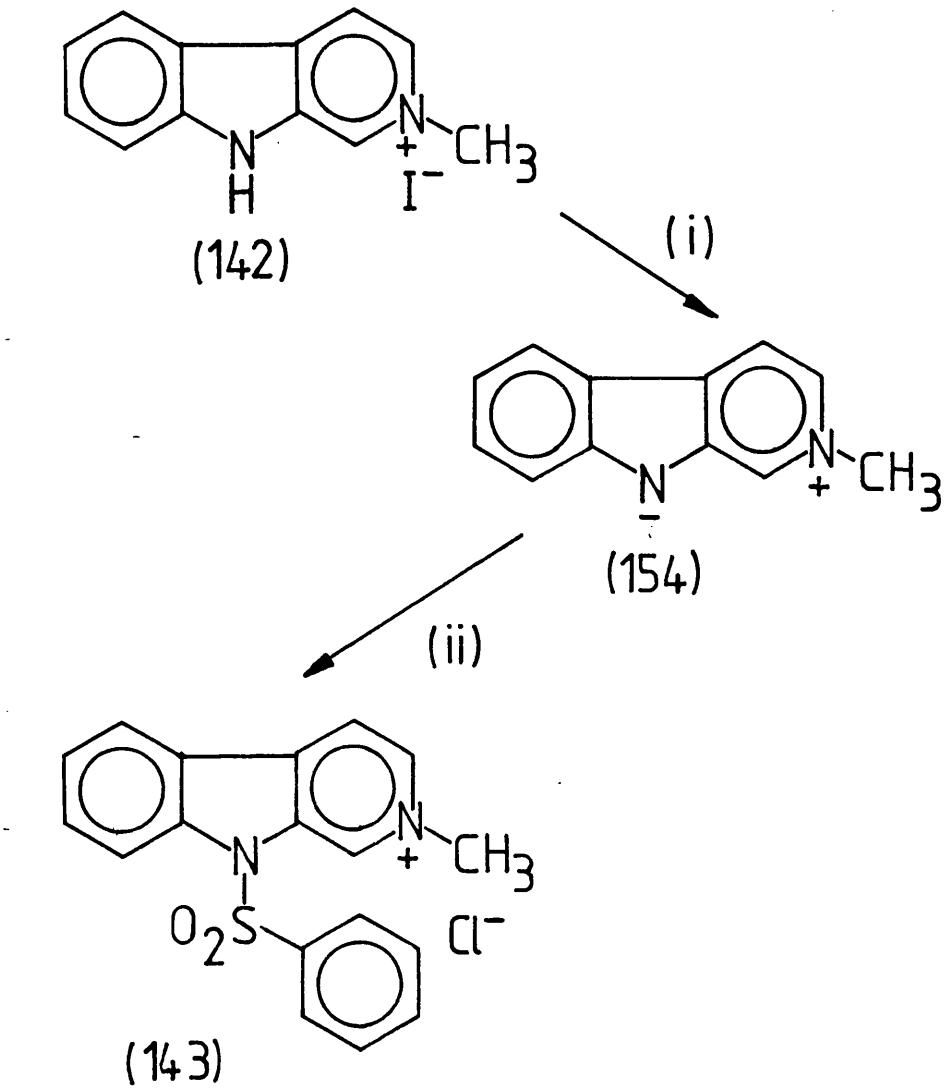
the benzenesulphonyl group did not usually interfere with the reactions of the indole ring. Therefore it was decided to base subsequent work in the carboline area on the 9-benzenesulphonyl-2-methyl-β-carbolinium salt (I43, R = $C_6H_5SO_2$).

From the facts reported above, the most obvious way of preparing the desired salt was the reaction of the anhydro-base derived from (I42) with benzenesulphonyl chloride. This was found to be the case; reaction in toluene gave the previously unknown 9-benzenesulphonyl-2-methyl-β-carbolinium chloride (I43, R = $C_6H_5SO_2$) in modest yield (53%). The compound had the expected spectral characteristics (Appendix I; spectra I-3) and gave a correct microanalysis. The procedure is outlined in Scheme IO.

Isoquinolinium salts (I27) can be reduced to I,2-dihydroisoquinoline (I) by sodium dithionite,[I79,I80] lithium aluminium hydride[I48,I8I] or dialkylaluminium hydrides.[I82] Lithium aluminium hydride is prefered[I8I] to sodium dithionite since it leads to purer products and this reagent will also reduce those salts that are inert to dithionite. I,2-Dihydroisoquinolines themselves are only slowly reduced by lithium aluminium hydride to form I,2,3,4-tetrahydroisoquinolines (I55).[I83]

When isoquinolinium salts are reduced with sodium borohydride under the usual aqueous-ethanolic solvent

Scheme IO.



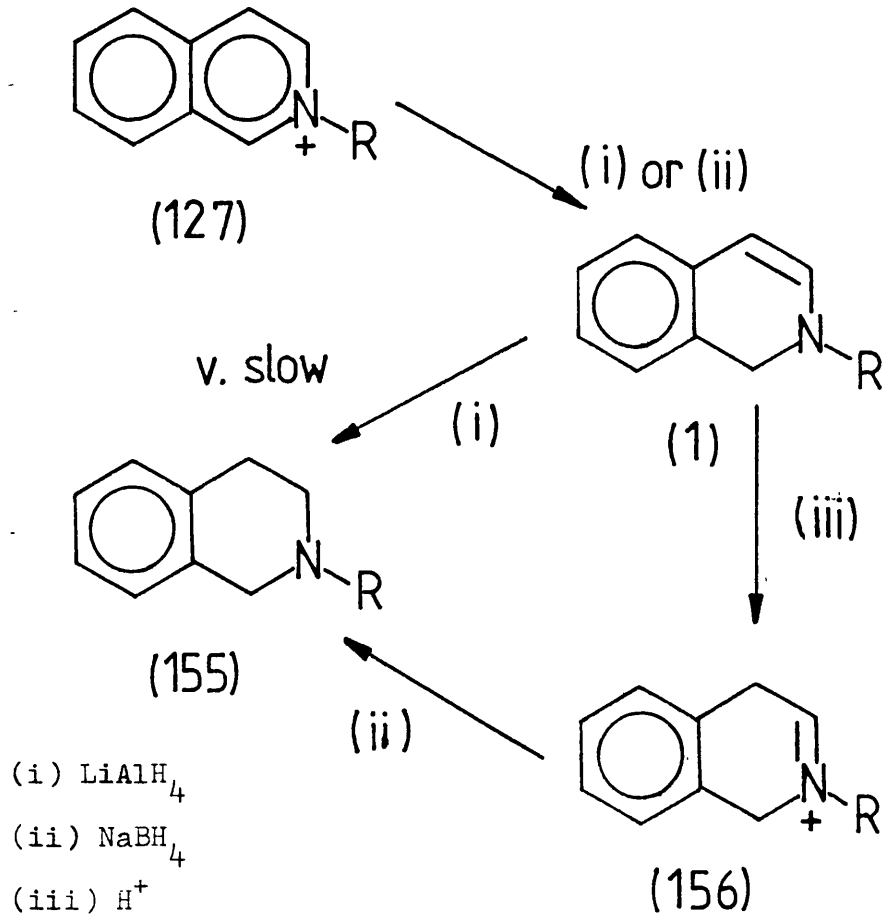
(i) NaOH, H_2O

(ii) $C_6H_5SO_2Cl$, Toluene

conditions, tetrahydroisoquinolines (I55) are produced. The I,2-dihydroisoquinoline (I) is formed first, and this can[I84] be protonated by the solvent to (I56) and reduced further to (I55). This is shown in Scheme II.

If a nonprotic solvent such as pyridine[I85] or dimethylformamide[I86] is used, then the I,2-dihydroisoquinoline can be isolated. In some cases the use of anhydrous methanol[I] enables selective reduction of the isoquinolinium salts to be achieved.

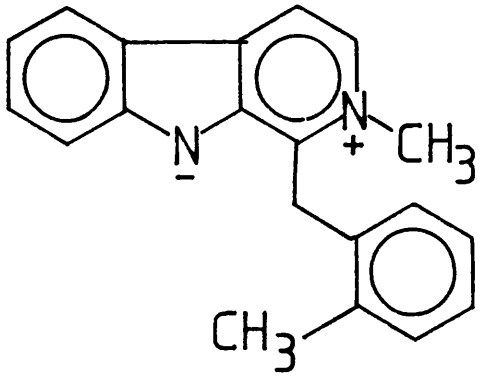
Scheme II.



No method for the partial reduction of a fully aromatic β-carboline to a dihydro- derivative has been described. The only instance where such a reduction may have occurred is in the reaction of the anhydro-base (I57), derived from 2-methyl-I-(2-methylbenzyl)-β-carbolinium iodide, with sodium dithionite. This reaction yielded a yellow, strongly reducing, fluorescent product which on hydrogenation gave 2-methyl-I-(2-methylbenzyl)-I,2,3,4-tetrahydro-β-carboline (I59). The nature of this substance, to which the structure (I58) was assigned as one possibility,[I87] has never been confirmed.

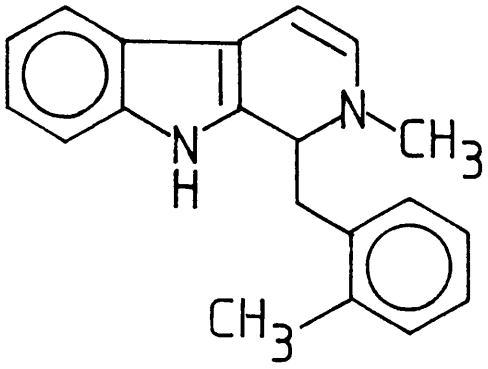
As lithium aluminium hydride has been the most widely used reducing agent for the partial reduction of isoquinolinium salts,[I46-9,I5I,I8I,I83] it was decided to use an identical procedure in order to attempt the partial reduction of the β-carbolinium salt (I43, R = $C_6H_5SO_2$) to the I,2-dihydro- species (I60).

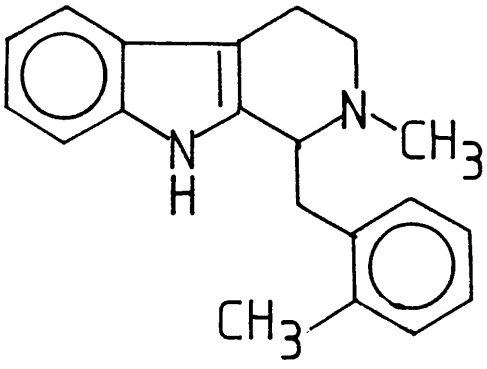
Accordingly a suspension of the quaternary salt (I43, R = $C_6H_5SO_2$) in ether was treated with an excess of lithium aluminium hydride under nitrogen and stirred at room temperature. In theory the yellow salt should have slowly dissolved in the ether to yield (a probably) colourless solution of the I,2-dihydro- compound, but even after stirring for 24 hours there appeared to be no decrease in the amount of salt present. The ultra-violet spectrum of the ether solution showed a complete absence



(157)

(158)





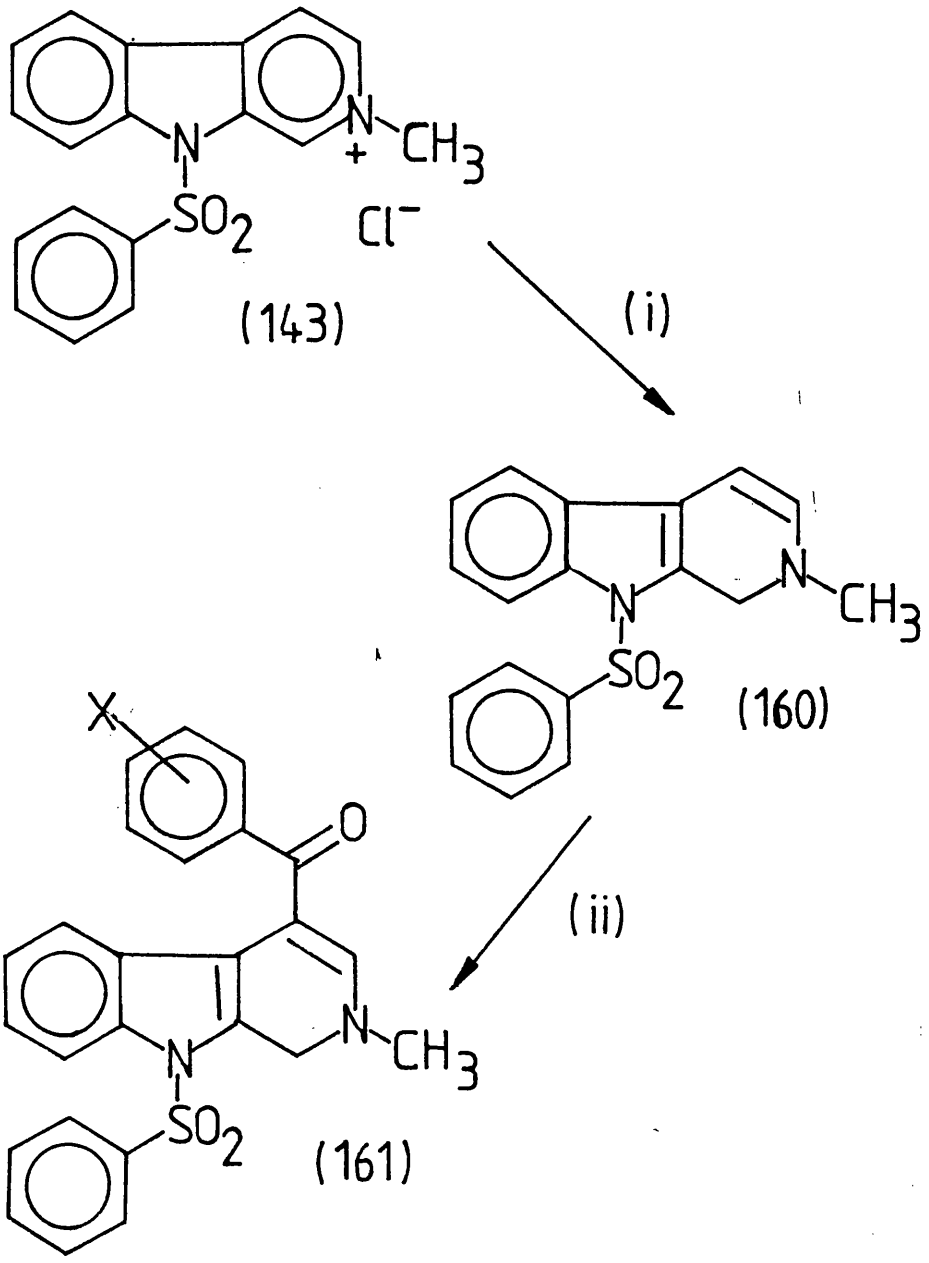
(159)

of absorption in the band λ 200 nm to 390 nm, indicating the complete absence of the I,2-dihydro- species (I60). Destruction of the lithium aluminium hydride with saturated potassium sodium tartrate solution and working up of the reaction gave an almost quantitative recovery of the quaternary salt (I43).

As the failure of (I43) to react with the reducing agent in ether may have been due to its lack of solubility, it was decided to repeat the procedure using tetrahydrofuran as solvent. The initial suspension of (I43) was pale yellow, indicating a slight solubility in tetrahydrofuran, but after stirring for a total of five hours the colour and solid (I43) had disappeared. The ultra-violet spectrum of this solution was totally different to that of the starting salt. The strong bands at λ_{max} 209, 2I8, 260, 30I and 348 nm, in ethanol, were replaced by weak and broad bands at λ_{max} 205, 238 and 288 nm (tetrahydrofuran).

After decomposition of the excess lithium aluminium hydride, the tetrahydrofuran solution was decanted off and dried over magnesium sulphate. All these procedures were carried out under an atmosphere of nitrogen - the solution rapidly turning orange-red on exposure to oxygen. The solution, after filtration, was reacted with triethylamine followed by benzoyl chloride, and stirred overnight. Working up of the reaction yielded a pale yellow solid, the TLC of which (silica, 9:I ethyl acetate-

Scheme I2.



(i) $LiAlH_4$, ether or tetrahydrofuran

(ii) ArCOCl, triethylamine or pyridine

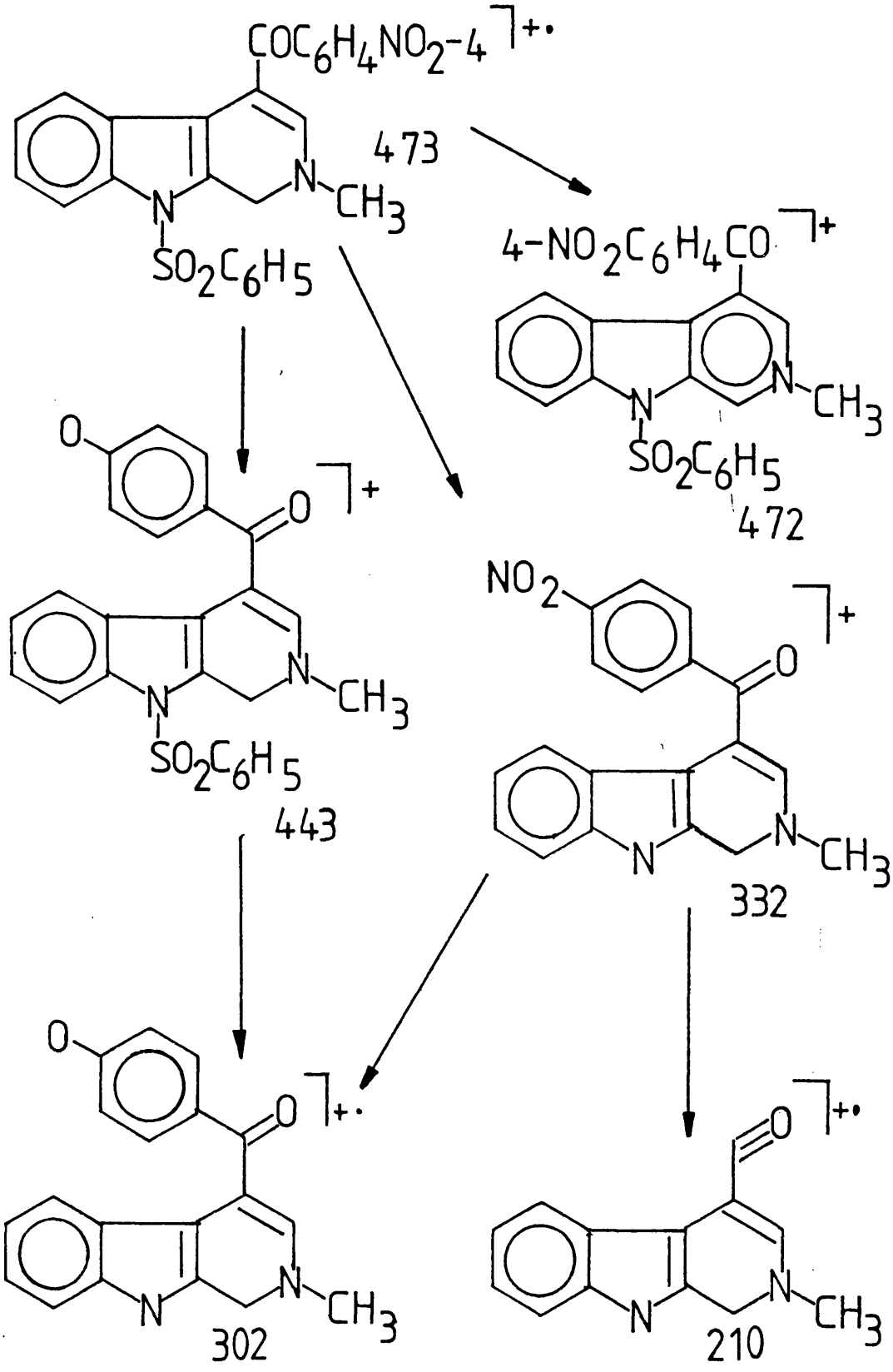
petroleum ether) showed it to be different from the starter (I43). The spectra, however, indicated that the product was benzoic acid derived from hydrolysis of the benzoyl chloride. The procedure described above is outlined in Scheme I2.

In the isoquinoline series 4-nitrobenzoyl chloride had given higher yields of the 4-substituted product than had benzoyl chloride itself. Repetition of the above procedures using 4-nitrobenzoyl chloride gave an orange solid in low yield. The infra-red and ^{1}HNMR spectra of this solid were inconclusive and of little value, but the mass spectrum (Appendix I, spectrum 4) afforded some encouragement.

Overall the peaks in the spectrum were few in number and of low intensity and detailed analysis of the break-down pattern was not really feasible. The parent ion, though weak, occurred at the correct mass number of m/z 473. There was a much larger peak at M-I corresponding to the aromatic species, formed by the loss of H$^{\bullet}$, and a larger than expected M+I peak indicating some ion-molecule interaction in the spectrometer.

The proposed fragmentation pattern is outlined in Scheme I3. The parent ion probably fragmented by the loss of nitrogen (II) oxide and a benzenesulphonyl radical to form the ion at m/z 302. This fragmentation could have occurred by two routes - loss of nitrogen (II)

Scheme I3.


COC6H4NO2-4 +·
473
N
CH3
SO2C6H5
4-NO2C6H4CO +
472
O
+
443
NO2
332
302
210

oxide, to form the ion at m/z 443, followed by loss of the benzenesulphonyl radical, or by loss of the benzenesulphonyl radical to form the ion at m/z 332 followed by loss of nitrogen (II) oxide. The ion at m/z 332 could also have lost a 4-nitrophenyl radical to give the ion at m/z 210. The base peak of the spectrum was at m/z 46 corresponding to NO_2^+.

The interpretation of the spectrum reported above was only speculative, but the presence of the parent ion at m/z 473 suggested that the reaction of 1,2-dihydro-β-carbolines with aromatic acid chlorides did indeed occur as predicted to yield the product (161, X = 4-NO_2). The problem was to improve the yield.

Several attempts to repeat the above reaction procedure ($LiAlH_4$/tetrahydrofuran/triethylamine/4-nitrobenzoyl chloride) produced no trace of the required product. Changing the acid chloride to 4-chlorobenzoyl chloride or 4-methylbenzoyl chloride gave none of the corresponding products (161, X = 4-Cl and 4-CH_3 respectively).

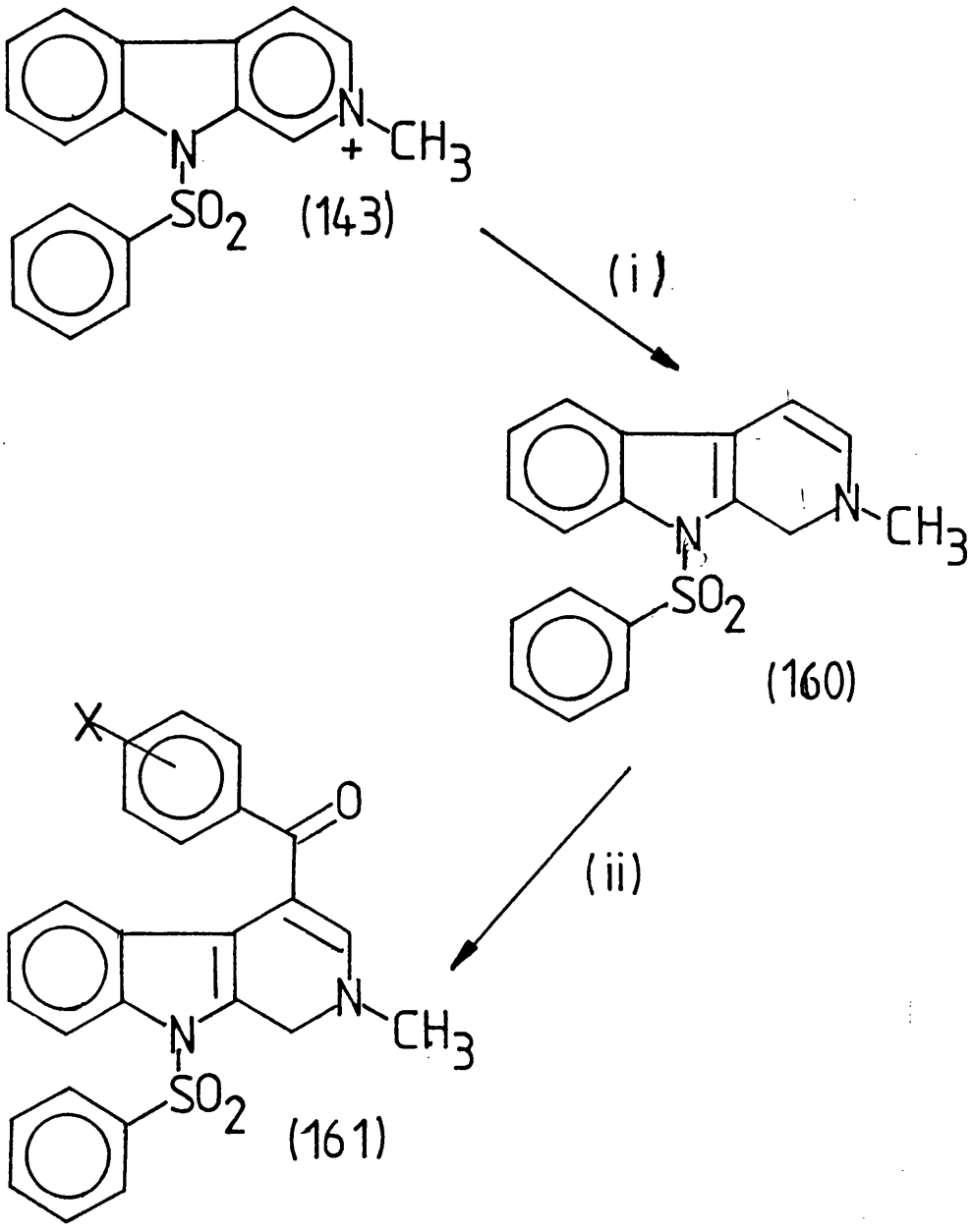
The use of pyridine as base in place of triethylamine gave a solid with 4-nitrobenzoyl chloride. The infra-red and ^{1}HNMR spectra were comparable with those of the solid from the triethylamine/4-nitrobenzoyl chloride reaction and the mass spectrum was identical. The yield, however, was still very low and the product gave an unsatisfactory microanalytical result and had an indefinate melting

point.

It appeared that the above reaction of the I,2-dihydro- compound with acid halides did not give satisfactory or consistent results. The intermediate I,2-dihydro compound (I60) was extremely unstable, particularly on contact with air, and the manipulative procedures required in its preparation, such as decanting off of the solution and drying over magnesium sulphate, led to its exposure to the atmosphere and therefore a loss of yield. What was needed were experimental conditions which avoided unnecessary manipulation and risk of exposure to the atmosphere.

It was mentioned earlier that isoquinolinium salts have been reduced to I,2-dihydroisoquinolines by sodium borohydride in dimethylformamide[I86] and it was decided to attempt an extension of this reaction to the β-carboline series. Consequently the quaternary compound (I43) was added to a suspension of sodium borohydride in dimethyl-formamide (Scheme I4) and the resulting colourless solutuon treated with triethylamine and 4-nitrobenzoyl chloride. Work up of the reaction and column chromatography afforded an orange solid. The product (I6I, X = 4-NO_2) proved to be a single spot by TLC but it had a very indistinct melting point. The compound had an infra-red absorption at ν_{max} I7I0 cm^{-I} and no absorption above 3000 $cm.^{-I}$

Scheme I4.



(i) $NaBH_4$, Dimethylformamide

(ii) ArCOCl, Triethylamine or Pyridine

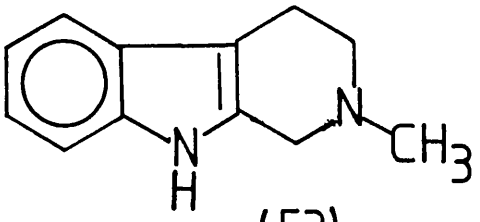
Compound (161) can be regarded as a vinylogous amide and the absorption at 1710 cm^{-1} is very high for an amide. It is however in the correct region for an aryl ketone.[188] The ^{1}HNMR spectrum was of little value, the peaks being very broad and ill-defined, although the integrals appeared to be in the correct ratio. No mass spectrum was determined.

After several further attempts at reductions using sodium borohydride in dimethylformamide with very little success it was decided to abandon this approach.

Some French authors had claimed to have isolated 1,2-dihydroisoquinolines from the reduction of isoquinolinium salts with sodium borohydride in aqueous methanol,[189] and this procedure along with that utilising anhydrous methanol[1] were investigated for the β-carboline series. In both cases, however, the only product isolated was shown to be 2-methyl-1,2,3,4-tetrahydro-β-carboline (53) from the Infra-red and ^{1}HNMR spectra (Appendix I, spectra 5-7) and comparison of the melting point with that in the literature.[116]

The benzenesulphonyl protecting group can be removed from indoles by the action of sodium hydroxide in aqueous methanol[177] and the sodium borohydride solution used in the reduction, or the borate solution produced in the work up, must have been sufficiently basic to remove the benzenesulphonyl group at some stage during the course

of the reaction.



(53)

It was becoming apparent that reactions involving 9-benzenesulphonyl-2-methyl-β-carbolinium chloride were not succeeding. Even though there was some evidence that the required product was formed in at least one case (I6I, X = 4-NO_2), the low yield indicated that only a partial reaction had occurred. This low yield could have resulted because the intermediate I,2-dihydro- compound (I60) was only partialy formed, or did not fully react, or decomposed prior to reaction with the acid chloride.

The ease of formation of (I60) was largely dependent on the solubility of the starting β-carbolinium salt in the reaction solvent and on the electron density at the I-carbon atom being sufficiently low to enable attack by a hydride ion. The latter fact could be influenced by the nature of the substituents in the molecule - the electron withdrawing benzenesulphonyl moiety on the indolic nitrogen possibly lowering the electron density in the molecule. It was also possible that lithium

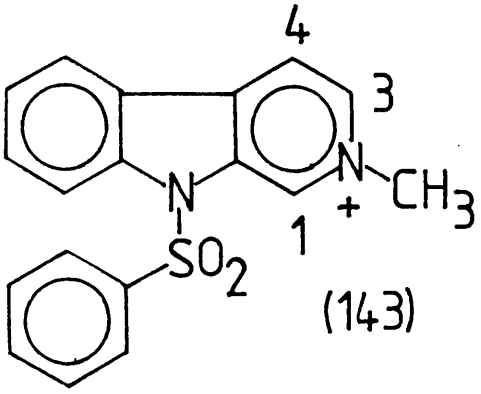
aluminium hydride could remove the benzenesulphonyl protecting group as sodium borohydride had done. This would result in the formation of the anhydro-base (II) in preference to the I,2-dihydro- species.

Substituents in the molecule would also effect the reactivity of the I,2-dihydro- compound. Electron withdrawing groups, such as benzenesulphonyl, on the indole nitrogen would lower the negative charge at the C-4 position in (I60b) and thus lower the reactivity of the molecule.

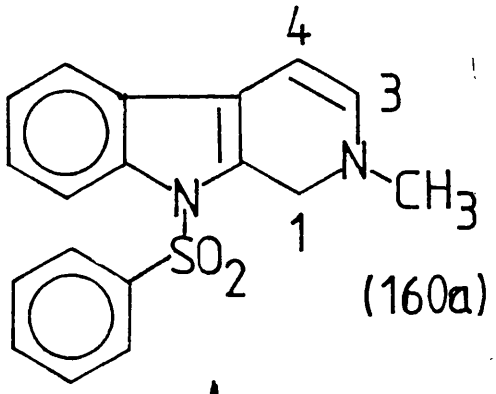
The instability of compound (I60) has already been touched on. I,2-Dihydroisoquinolines are well known[I] for their ease of oxidation and ease of disproportionation to a mixture of the fully aromatic and tetrahydro- species and there is no reason to believe that this process does not occur in the β-carbolines. This reactivity should not be readily effected by substituents on the ring but more by manipulative procedures in the course of the reaction.

It was decided eventually that the electron withdrawing character of the benzenesulphonyl group was having too great an effect on the reactivity of the I,2-dihydro- species (I60) and another substituent on the indolic nitrogen atom was desirable.

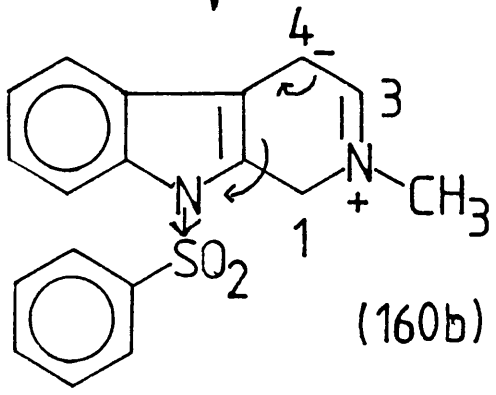
The simplest substituent which would have the smallest effect on the β-carboline ring system was a methyl group. The only disadvantage was that an indole nitrogen is



(143)



(160a)



(160b)

extremely difficult to demethylate.

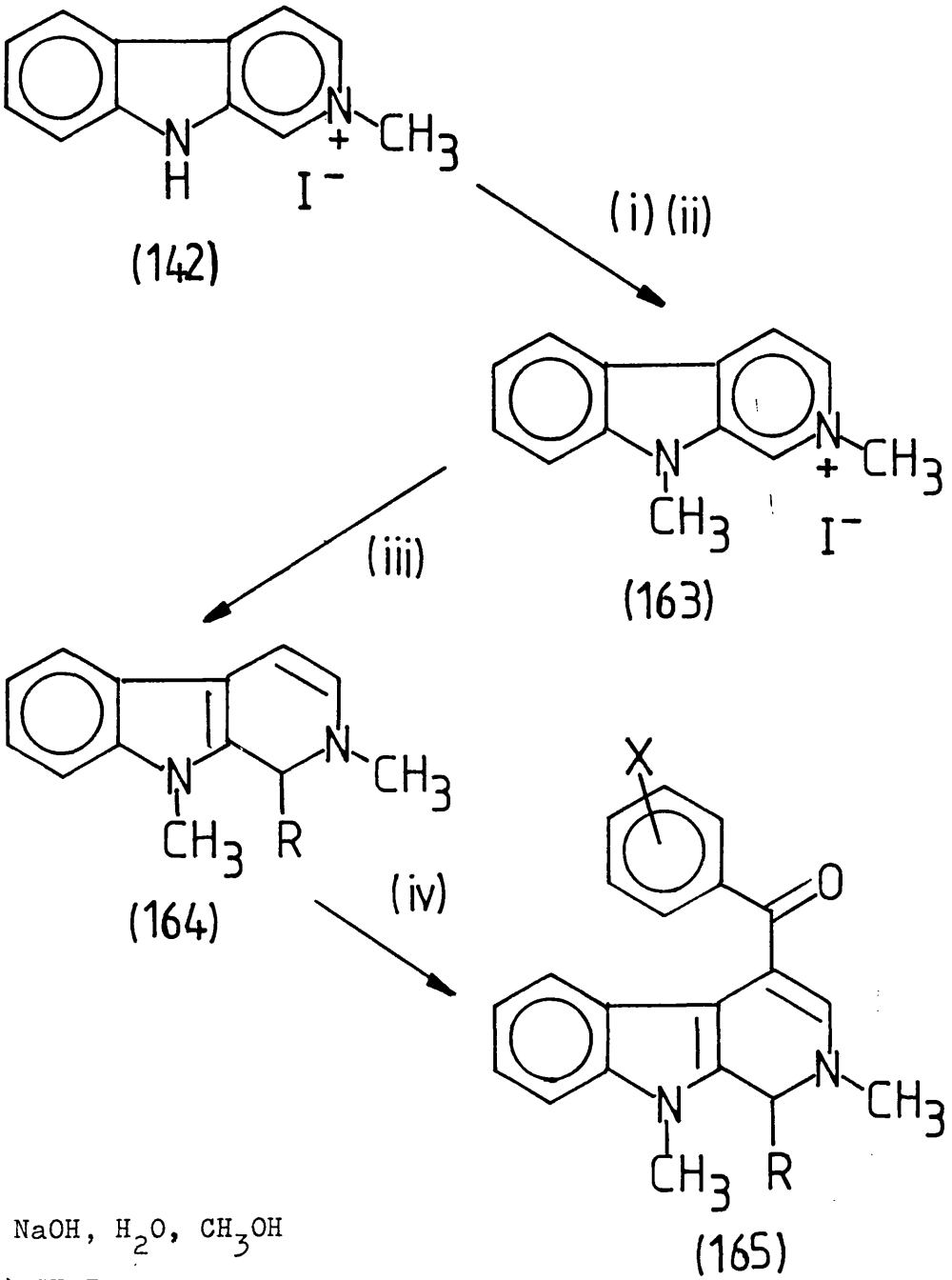
Accordingly 2-methyl-β-carbolinium iodide was alkylated with iodomethane, according to a literature procedure, to give 2,9-dimethyl-β-carbolinium iodide (I63) and this was subjected to partial reduction. The synthetic route is outlined in Scheme I5.

Of all the attempts involving the use of lithium aluminium hydride (in tetrahydrofuran or ether) followed by treatment with pyridine or triethylamine, then by treatment with benzoyl, 4-chlorobenzoyl, 4-nitrobenzoyl or 3,5-dinitrobenzoyl chlorides, only the combination of tetrahydrofuran/triethylamine/benzoyl chloride produced any result and then only once in numerous attempts. On no occasion was there any evidence from the ultra-violet spectrum of the intermediate reduction product to indicate the presence of the I,2-dihydro- species (I64, R = H).

The one tangible product formed in the above case (I65, R = X = H) was a dark oil which could not be decolourised by boiling with activated charcoal or purified by column chromatography. It did not solidify and ultra-violet, infra-red and proton NMR spectroscopy afforded very little data about it, save that it was not starting material or a simple derivative of benzoic acid.

The mass spectrum contained a peak at m/z 302 which could be atributed to the required parent

Scheme I5.



(i) NaOH, H_2O, CH_3OH

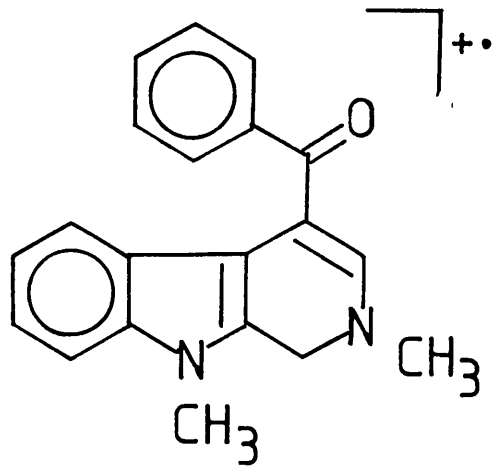
(ii) CH_3I

(iii) $LiAlH_4$, ether or Tetrahydrofuran

(iv) ArCOCl, Triethylamine or Pyridine

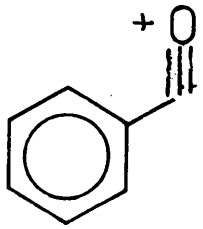
ion (I65, R = X = H) and a relatively abundant peak at m/z 303 suggesting an ion-molecule interaction. The base peak of the spectrum occurred at m/z 105 corresponding to the phenylacylium ion (I66) and there was a strong peak at m/z 77 indicating the presence of the phenyl cation (I67). Very little further information could be deduced from the other, rather weak peaks in the spectrum, except that the peak at m/z 210 could be due to the ion (I68).

Therefore the evidence that 2,9-dimethyl-β-carbolinium iodide (I63) had reacted with lithium aluminium hydride in tetrahydrofuran and then with benzoyl chloride to give the correct product was far from conclusive. The fact that any product was only isolated on one occasion suggested that the procedure of reduction with lithium aluminium hydride followed by treatment with an acid chloride was not going to provide a satisfactory route to the required acylated 1,2-dihydro-β-carboline (I65).



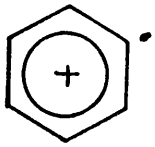
(165 R=X=H)

m/z 302



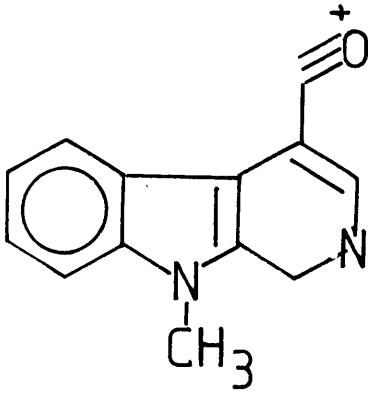
(166)

m/z 105



(167)

m/z 77



(168)

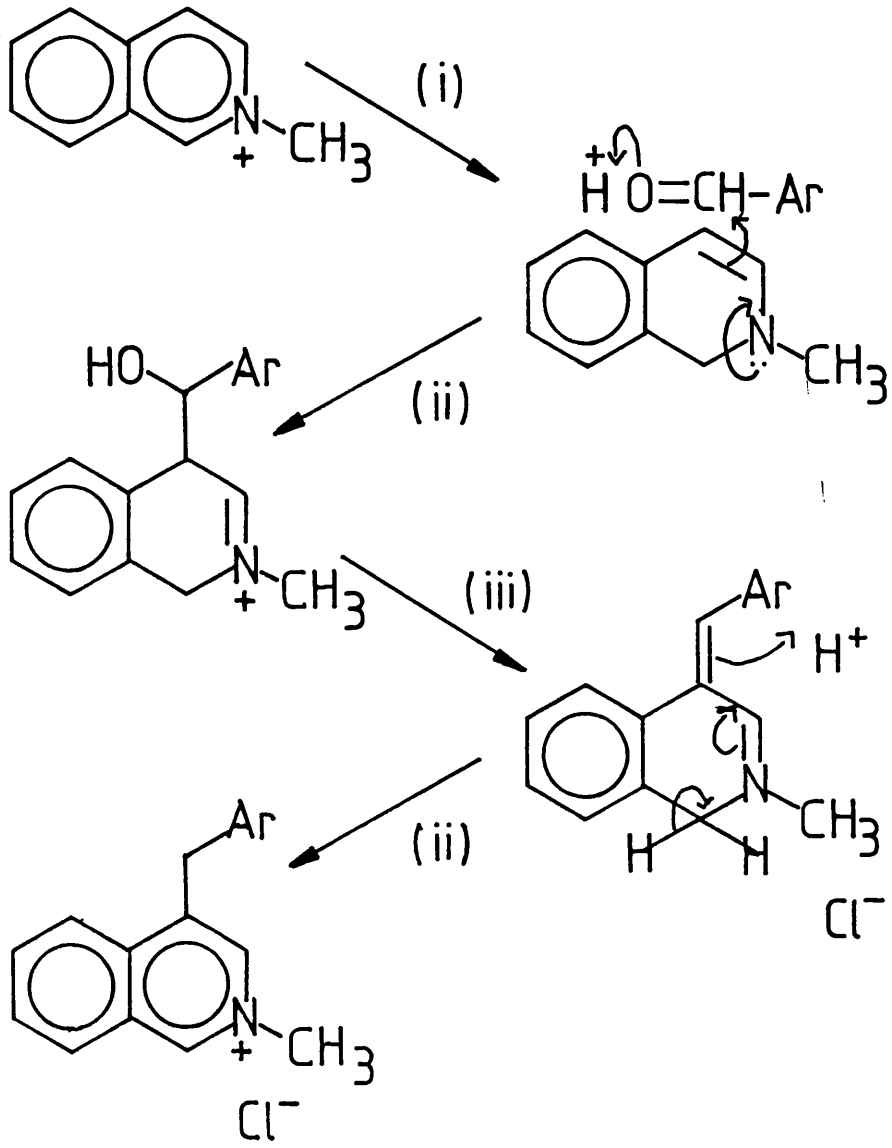
m/z 210

As mentioned at the begining of this discussion I,2-dihydroisoquinolines (I) will react with aromatic aldehydes in acid solution to afford 4-benzyl-isoquinolinium salts (I3I).[I49] The proposed mechanism is outlined in Scheme I6.[I,I49]

In order to ascertain whether the lack of success so far was due to the failure of the lithium aluminium hydride to attack the carbolinium salt (I63) or whether the I,2-dihydro- species (I64) was failing to react with the acid chloride, it was decided to repeat the reaction with aldehydes in place of acid chlorides. Accordingly 2,9-dimethyl-β-carbolinium iodide (I63) was reduced with lithium aluminium hydride and the resulting solution treated with acetic acid, then with 4-nitrobenzaldehyde and finally with perchloric acid. The procedure is outlined in Scheme I7.

The reaction yielded a red solid in low yield. The lack of an absorption in the region of ν_{max} I690 - I7I5 cm^{-I} in the infra-red spectrum of the solid indicated that the product was not 4-nitrobenzaldehyde. The only absorption in the carbonyl region of the spectrum was at ν_{max} I640cm^{-I} possibly due to a $C{=}N^{+}$ unit. The expected strong band at approximately I250 cm^{-I} characteristic of perchlorate salts, was not readily apparent. The melting point of 200-5°C was much higher than that of 4-nitrobenzaldehyde and more typical of a salt. Unfortunately the ^{I}HNMR

Scheme I6.[I,I49]

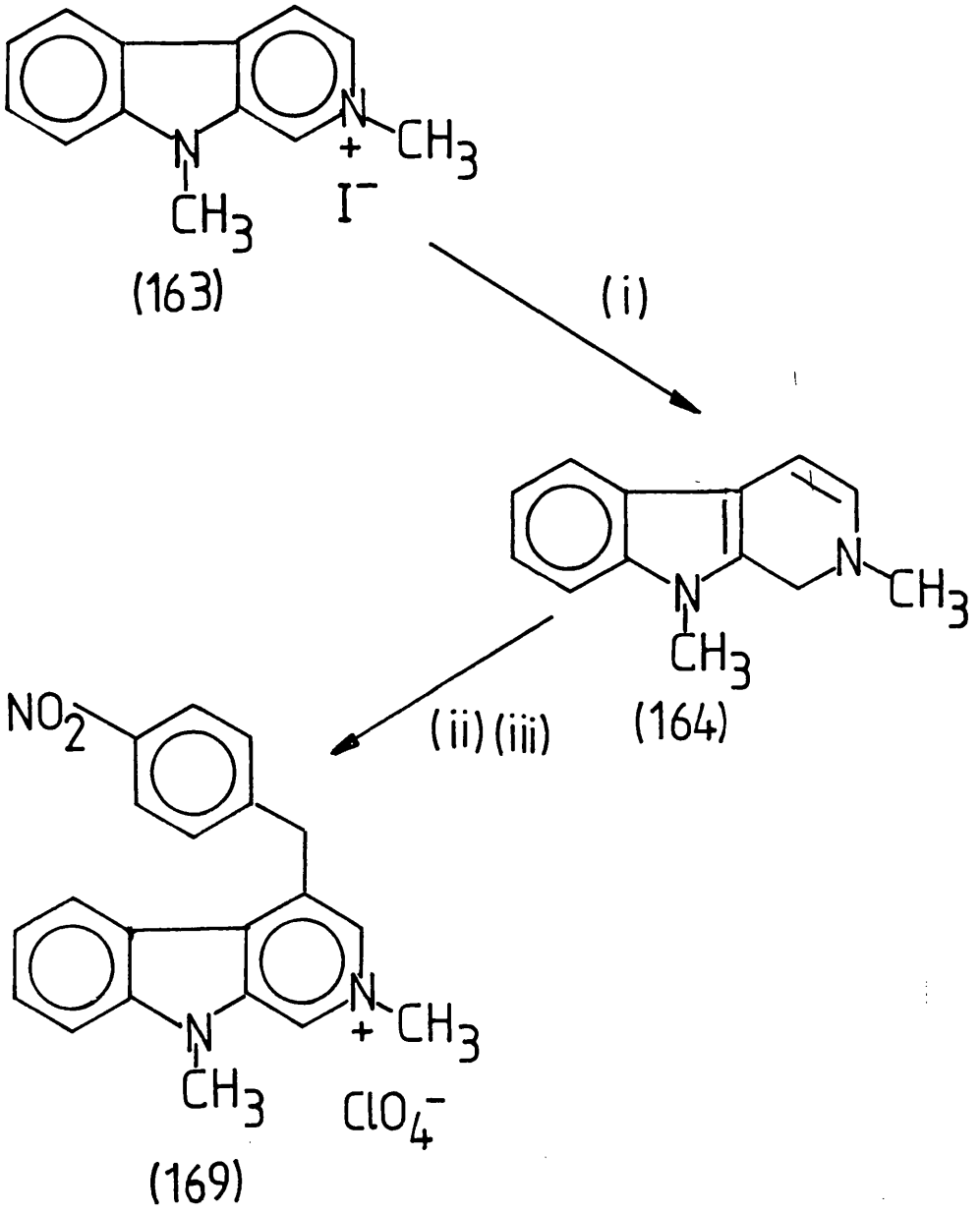


(i) $LiAlH_4$, Ether

(ii) HCl

(iii) - H_2O

Scheme I7.

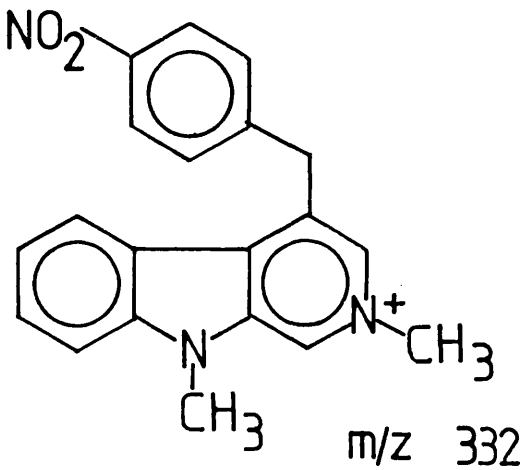


(i) $LiAlH_4$, Tetrahydrofuran

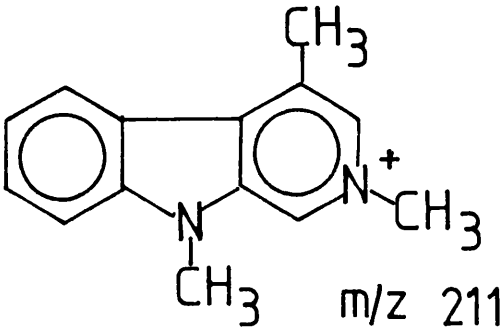
(ii) ArCHO, CH_3CO_2H

(iii) $HClO_4$, CH_3OH

spectrum was unresolved and the only positive evidence in favour of the desired product (I69) was from the mass spectrum which showed an extremely weak peak corresponding to the parent ion (I69) at m/z 332. The base peak was at m/z 44 and the only other prominent peak occurred at m/z 2II corresponding to the ion (I70), formed by loss of the 4-nitrophenyl radical with proton acquisition.



(169) m/z 332



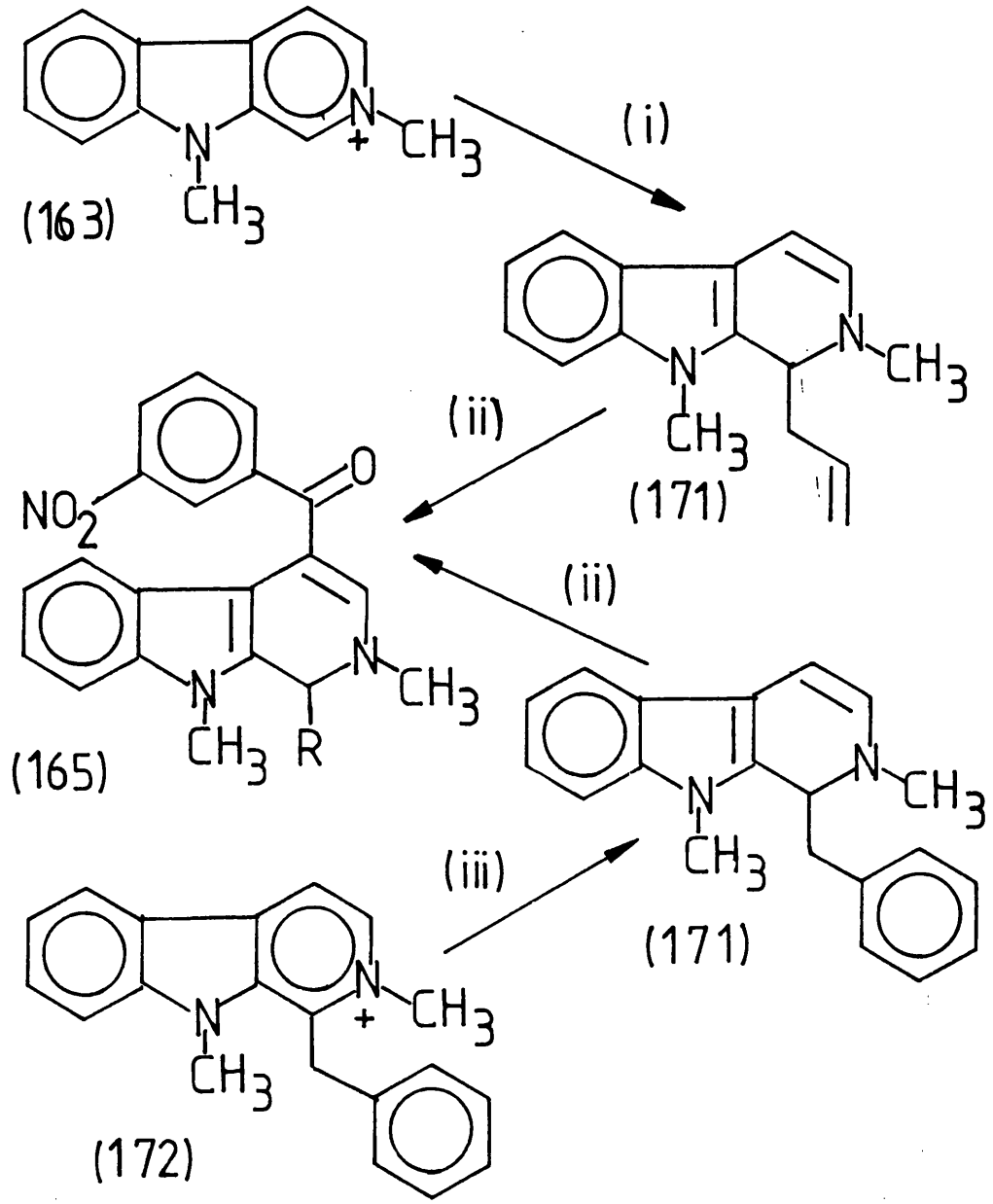
(170) m/z 211

These rather inconclusive results suggested that reactions of the β-carbolinium salts with lithium aluminium hydride and an aromatic aldehyde would be no more successful than those with acid chlorides. This approach was consequently abandoned. The similarity in poor yields between the acid chloride and aldehyde reactions suggested that it may have been the reduction stage which was causing the problems. Therefore, several other reducing agents were investigated in place of lithium aluminium hydride.

The ether soluble aluminium derivative sodium dihydrobis-(2-methoxyethoxy)-aluminate was tried with no success. The use of sodium borohydride in dimethylformamide also failed to give any product resembling a I,2-dihydro-β-carboline.

In a private communication and subsequent publication Knabe and Saggau claimed[190] that 2,9-dimethyl-β-carbolinium iodide could be reacted with allyl magnesium chloride to produce the I-allyl-2,9-dimethyl-I,2-dihydro- species (I7I, R = $CH_2CH\ \ CH_2$) which could then be reacted 3-nitrobenzoyl chloride and triethylamine to produce the product (I65, R = $CH_2CH=CH_2$, X = 3-NO_2).in 84% yield. The product had the correct microanalytical values. These authors also reacted I-benzyl-2,9-dimethyl-β-carbolinium iodide (I72) with lithium aluminium hydride in ether - tetrahydrofuran (I:I) to produce the I,2-dihydro- species

Scheme I8.



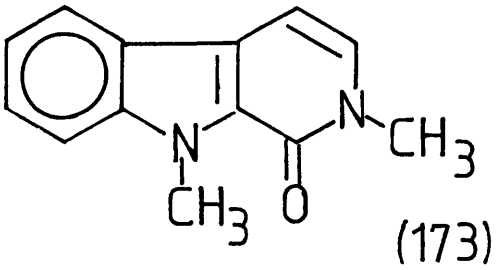
(i) $CH_2{=}CHCH_2MgCl$, Ether

(ii) $3\text{-}NO_2C_6H_4COCl$, Triethylamine

(iii) $LiAlH_4$, Ether-Tetrahydrofuran (I:I)

(I7I, R = $C_6H_5CH_2$) which they then reacted with 3-nitrobenzoyl chloride and triethylamine to produce (I65, R = $C_6H_5CH_2$, X = 3-NO_2) in 72% yield. The sequence of events is outlined in Scheme I8.

These claims suggest that the problems encountered in the work so far described may in fact be due to instability of the intermediate dihydro- compound (I64, R = H). The I-substituted compounds used by Knabe and Saggau should be more resistant to disproportionation and particularly oxidation to the amide (I73) than the unsubstituted compound.



(173)

The work described by these authors also shows that the β-carbolinium salt is susceptible to attack by nucleophiles other than hydride ion.

Bearing this in mind it was decided to investigate the reaction of 2,9-dimethyl-β-carbolinium iodide with n-butyl-lithium, in the hope of forming (I64, R = C_4H_9), and then to react this product with a benzoyl chloride to yield the I,2-dihydro- compound (I65, R = C_4H_9, X = H).

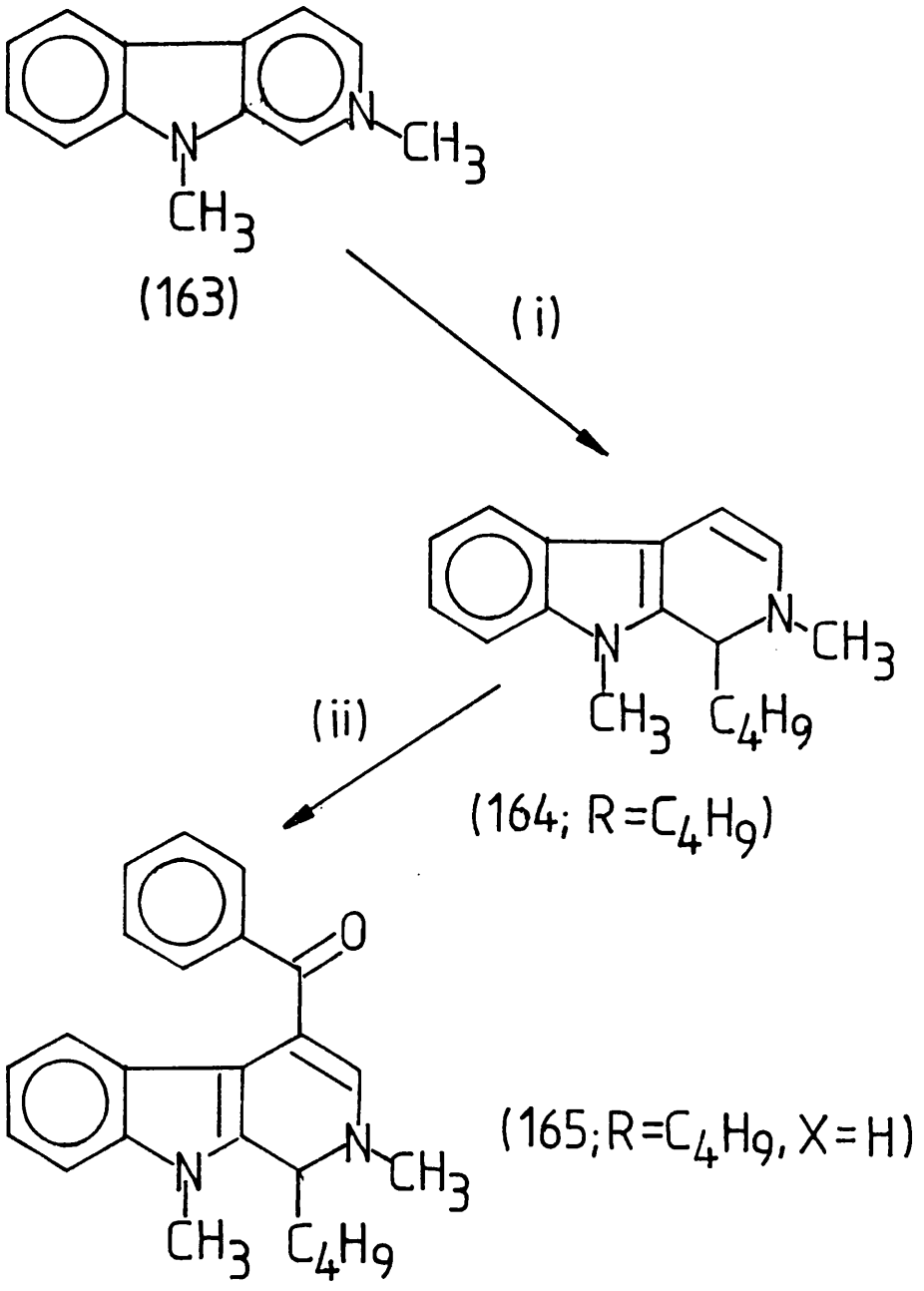
In practice the reaction (Scheme I9) afforded a yellow solid in 84% yield. The ultra-violet spectrum had bands at λ_{max} 267, 3I4 and 400 nm which corresponded with those described by Knabe and Saggau for the I-allyl-compound (λ_{max} 242, 270, 3I0 and 395 nm[I90]).

The infra-red spectrum exhibited two bands at ν_{max} I640 and I660 cm^{-1} the lower of which could have been an aromatic absorption and the higher one due to the vinylogous amide system present in the product. Once again, as in all of these carboline compounds, the ^{1}HNMR spectrum was unresolvable.

The mass spectrum, however, provided the best evidence as to the nature of the product (Appendix I, spectrum 8). The parent ion occurred at m/z 358 along with a much stronger than expected M-I peak corresponding to the aromatic species (I74). The base peak of the spectrum was at m/z 300 and could be atributed to the ion (I75) formed by loss of the butyl group from the ion (I74); a peak at m/z 30I corresponded to the loss of butyl from the parent ion. There were strong peaks at m/z 343/342, 329/328 and 3I5/3I4 corresponding to the loss of the alkyl homologs $CH_3^{\bullet}$, $C_2H_5^{\bullet}$ and $C_3H_7^{\bullet}$.

There appeared to be no obvious fragmentation pattern for the degradation of the ions at m/z 30I/300, but the peak at m/z I05, corresponding to the phenyl-acylium ion (I66), suggested that a stable radical such

Scheme I9.



(i) C_4H_9Li, Tetrahydrofuran

(ii) C_6H_5COCl, Triethylamine

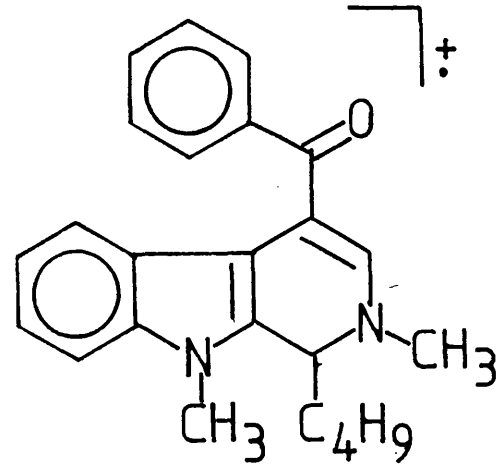
as (I76) could be formed. However, there was a peak at m/z 7I corresponding to the ion $C_5H_{II}^+$ and weak peaks at m/z 287/286 indicating loss of C_5H_{II} from the parent ion. The possible degredation pattern is outlined in Scheme 20.

This evidence seemed encouraging but the compound failed to give satisfactory microanalytical results, even after repeated recrystallisations and attempts at column chromatography, so that the mature of the product could not be proved conclusively. Attempts to repeat the procedure with other acid chlorides led to similar inconclusive results.

The failure to obtain any definite and substantial results from the reactions of 9-benzenesulphonyl-2-methyl-β-carbolinium chloride (I43) and 2,9-dimethyl-β-carbolinium iodide (I63) with reducing agents, indicated that attempts to prepare 4-substituted-β-carboline derivatives by partial reduction of a β-carbolinium salt was not a viable synthetic procedure.

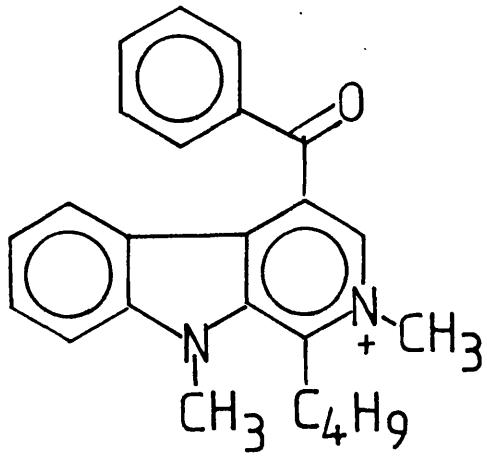
The synthetic procedure used in the preparation of the unsubstituted I,2-dihydro-β-carbolines carries a great risk of atmospheric oxidation. Wheras I,2-dihydro-isoquinolines are relatively stable the products from the β-carbolines are not. When exposed to air they form resins and tend to give complex products. Even when a successful reaction seems to be in sight the products

Scheme 20.

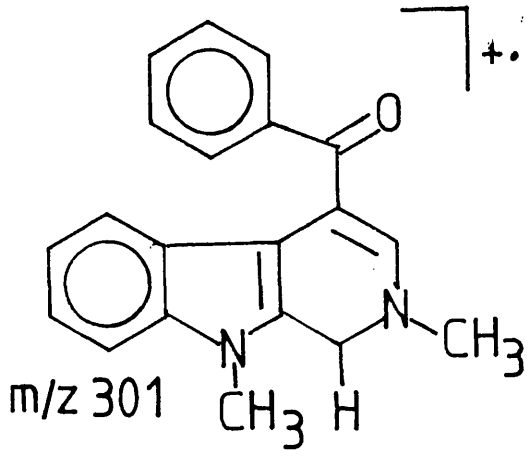


(165; R=C_4H_9, X=H)

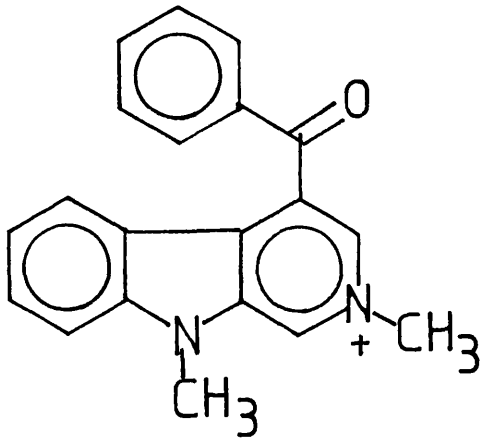
m/z 358



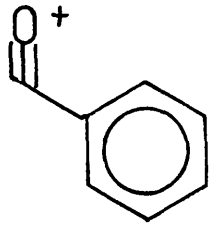
(174) m/z 357



m/z 301

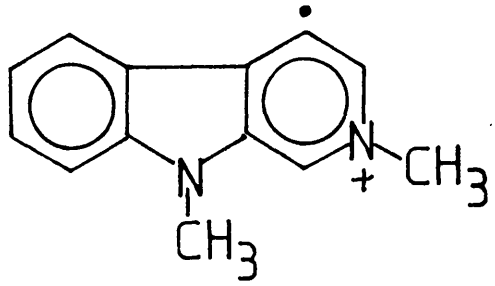


(175) m/z 300



(160) m/z 105

+

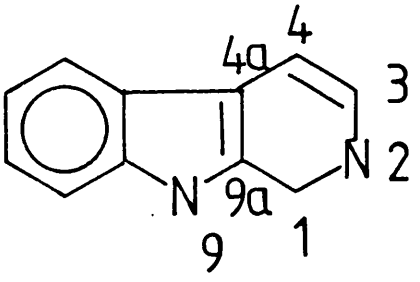


(176)

obtained are contaminated with materials which are extremely difficult to remove and meaningful results are hard to come by.

It would appear that the second enamine system formed by the presence of the indolic nitrogen atom (N-9) and indolic double bond (4a-9a), interacts with the primary enamine system under investigation to cause an increase of reactivity. This cross - conjugation of the two enamine systems results in the I-position being ripe for radical formation and hence resinification. If the position is blocked, as it is in the compounds described by Knabe and Saggau[190] and in the I-butyl compound described in this thesis, the reaction affords a more successful result. The fact that the reactions of Knabe and Saggau gave good yields of the desired products suggests that the interaction of the two enamine systems does not, however, effect the electron density and hence the nucleophilic character of the primary enamine system.

In the light of these observations it was decided to abandon this approach to the synthesis of 4-substituted -β-carboline derivatives.

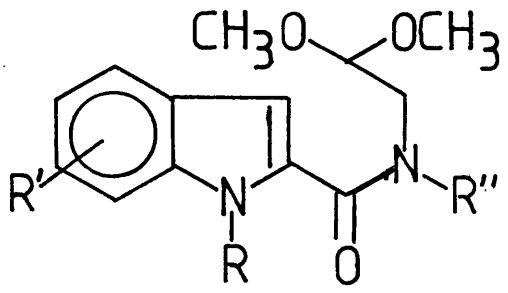


It was noted at the beginning of this discussion that I,2-dihydroisoquinolines can be obtained by the acid catalysed cyclisation of benzylaminoacetaldehyde dialkylacetals (I32) in ethanol,[I50] which can subsequently be reacted with aromatic aldehydes to afford 4-benzyl-substituted isoquinolinium salts (I35). The reaction, which is outlined in Scheme 2I, has been extensively investigated[I9I,I92] and the catalysts varied.[I93,I94] Under certain conditions the 4-hydroxy- (I77)[I95] and 4-alkoxy- (I78)[I96] tetrahydroisoquinolines have been obtained as intermediates.

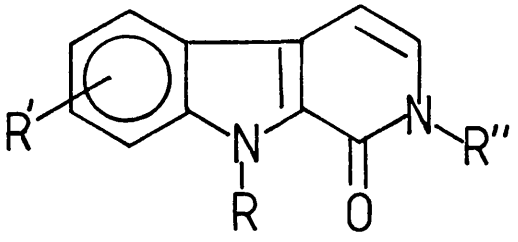
A proposed scheme for the application of this chemistry to the β-carboline series is outlined in Scheme 22. This particular reaction scheme had never before been used in the β-carboline ring system and all the intermediate compounds were novel.

The only similar chemistry known in the carboline area was the cyclisation of the oxo-compound (I82). In this case the course of the cyclisation depended on the nature of the substituents in (I82),[I59,I97,I98] for example, if the indole nitrogen was alkylated then the sole product was of the type (I83) irrespective of the nature of R' and R". However, if the indole nitrogen was unsubstituted then the nature of R' and R" became important. When R" was a hydrogen atom the product was exclusively the indolo-[I,2-a]-pyrazinone (I84) irrespective of the nature of R'. If R" was a methyl

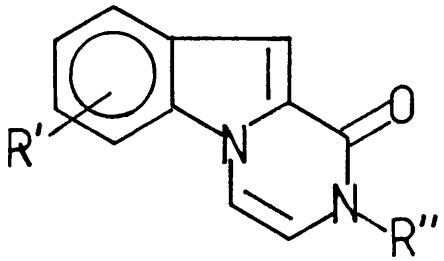
group then the product was usually the I-oxo-I,2-dihydro-β-carboline (I83), although if R' was an electron donating group one could obtain both types of product. One suspects that in such reactions the "conformational" preferences of the amide groups (which have considerable double bond character) influence the regioselectivity of the cyclisation. In any event these results suggested that in order to make certain of the correct cyclisation reaction, the intermediate (I8I) in Scheme 22 should carry a methyl group on the amide nitrogen atom (I8I, R = CH_3).



(182)

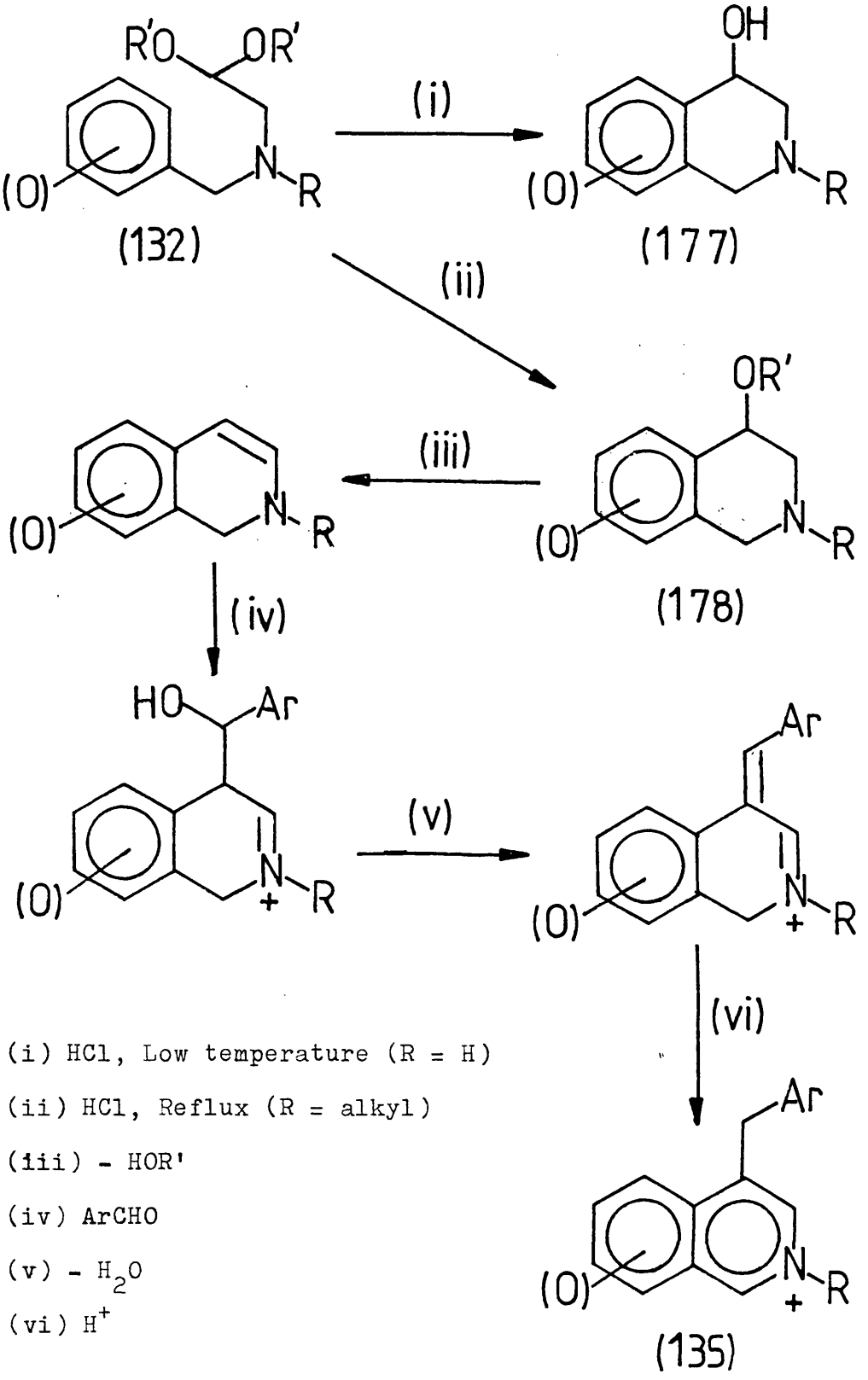


(183)



(184)

Scheme 2I.



(i) HCl, Low temperature (R = H)

(ii) HCl, Reflux (R = alkyl)

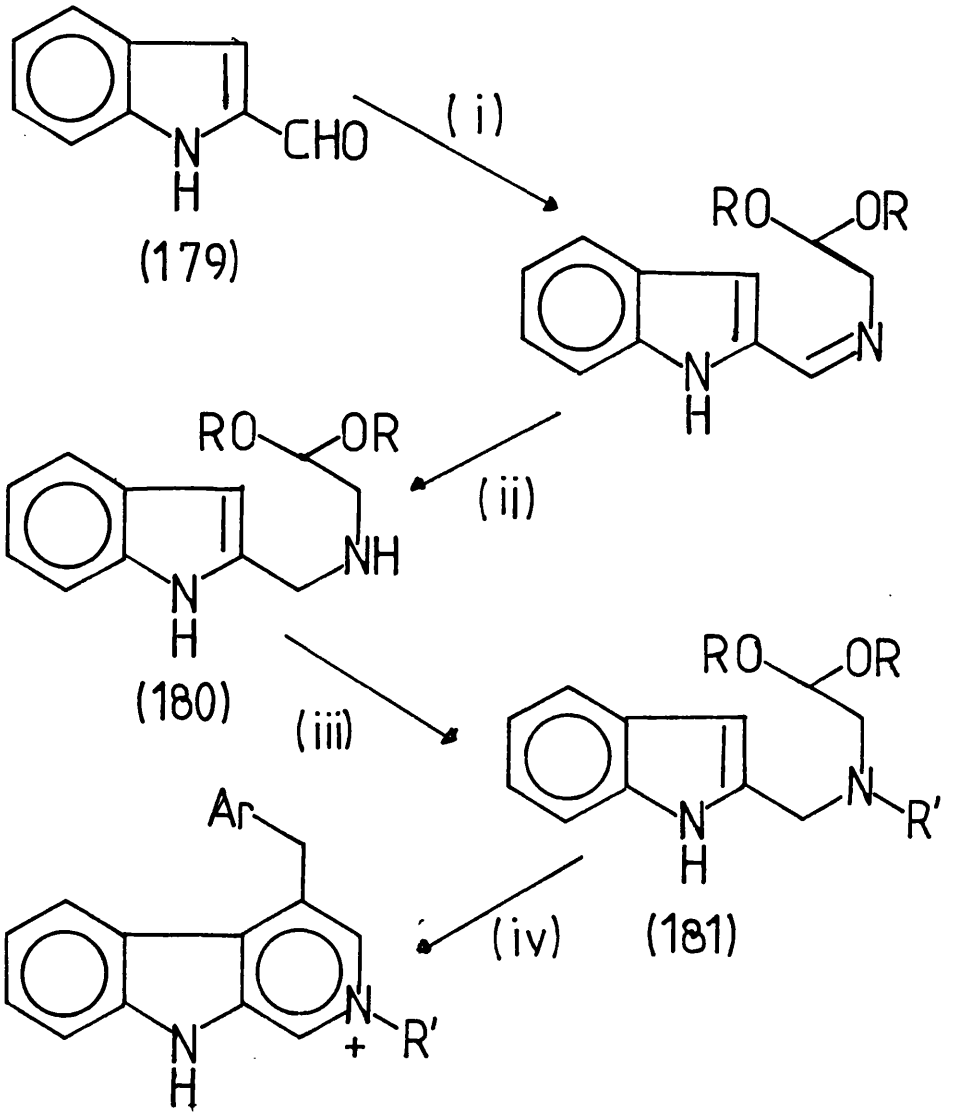
(iii) - HOR'

(iv) ArCHO

(v) - H_2O

(vi) H^+

Scheme 22.



(i) $(RO)_2CHCH_2NH_2$, Toluene, $4\text{-}CH_3C_6H_4SO_2OH$

(ii) $NaBH_4$, Ethanol

(iii) RX

(iv) ArCHO, H^+

The only forseeable difficulty with the proposed synthetic route in Scheme 22 was the stability and availability of the starting indole-2-carboxaldehyde (I79). Whilst indole-3-carboxaldehyde can be obtained in very high yield by simple formylation of indole,[I99] the 2-carboxaldehyde is not readily accessible. It has been prepared in poor yield by the oxidation of 2-hydroxymethylindole with either potassium permanganate in acetone[200] or with activated manganese dioxide.[201] Various substituted indole-2-carboxaldehydes have been prepared in moderate to good yields by the basic hydrolysis of indole-2-carboxylic acid 4-toluenesulphonylhydrazides, but the yield of indole-2-carboxaldehyde itself is poor.[202-3] In order to avoid the shortages of starting material that plagued the work on the partial reduction of the β-carbolinium salts, a better route to (I79) was sought.

Previously mention had been made of the work of Sundberg and Russell on syntheses utilising N-protected-2-lithioindoles.[177] Amongst the various substituted indoles prepared, the N-methoxymethyl- and N-benzenesulphonyl-indoles were shown to be satisfactorily lithiated in the 2-position and to give addition reactions with typical carbonyl and cyano compounds. Amongst these reactions was that with N-formyl-N-methylaniline to afford the substituted indole-2-carboxaldehyde.

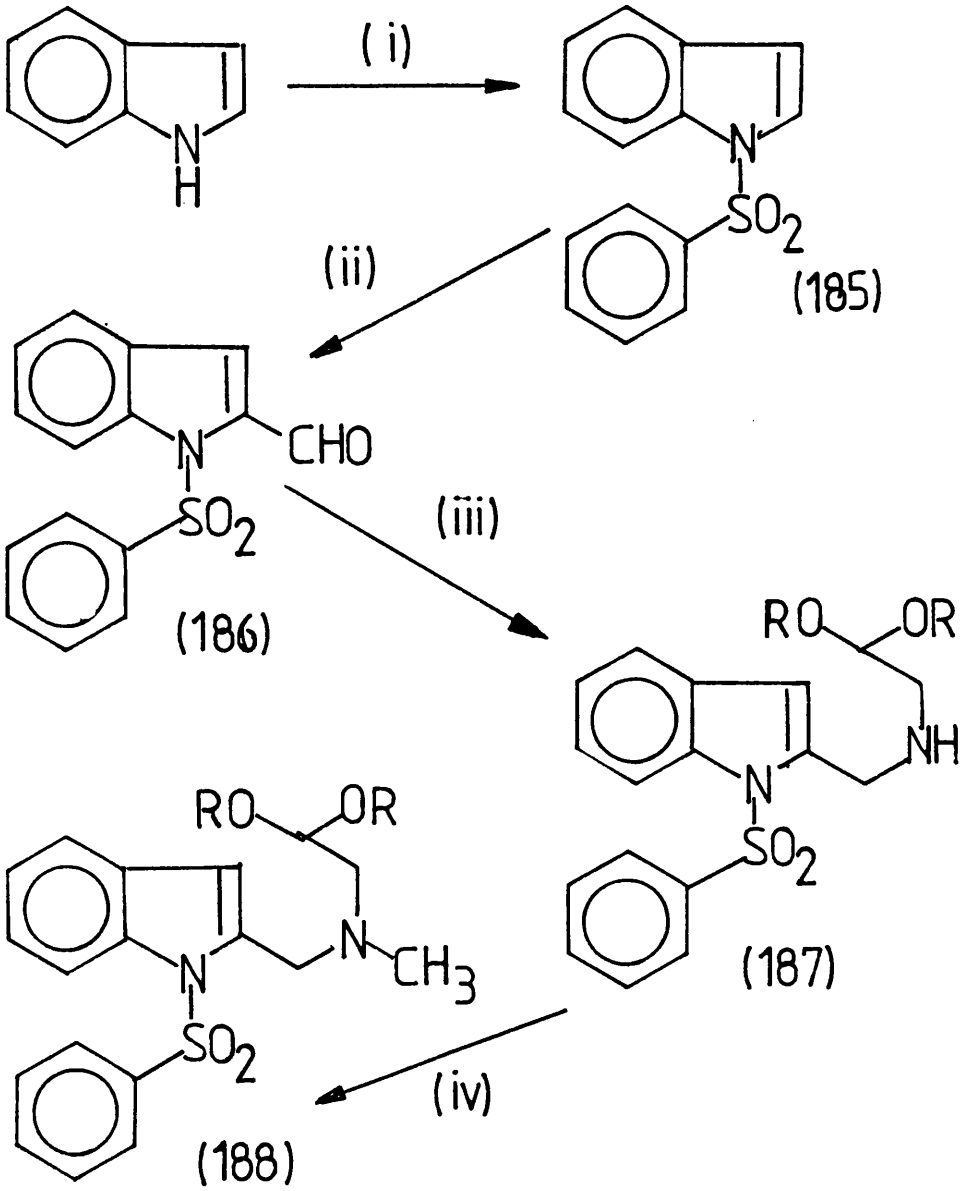
As mentioned earlier the benzenesulphonyl protecting

group has advantage in its ease of removal, but I-benzenesulphonylindole-2-carboxaldehyde (I86) was surprisingly absent from the list of compounds prepared by Sundberg and Russell, only the I-methoxymethylindole derivative was prepared in 46% yield. There was also no indication that these authors had tried to prepare the required compound (I86) and had failed. At this point then we decided to attempt the preparation of I-benzene-sulphonylindole-2-carboxaldehyde and to use it in a revised synthetic approach outlined in Scheme 23.

Accordingly I-benzenesulphonylindole was prepared following the literature procedure.[177] Indole was added to the sodium salt of dimethyl sulphoxide, prepared from sodium hydride in the usual way,[204] followed by addition of the sulphonyl chloride. The yields were, however, lower than reported in the literature (64% versus 92%). After some experimentation with other conditions, such as potassium hydroxide in dimethyl sulphoxide[205] and the use of hexamethylphosphoramide as cosolvent,[206] it was found that excellent results could be obtained simply by the use of 50% sodium hydride in tetrahydrofuran. The use of ether or dioxan as solvent also gave excellent yields.

The product obtained was identical to the literature compound in terms of melting point and spectral data. The ^{1}HNMR was consistent with that expected for the structure although the resolution was better than reported

Scheme 23.



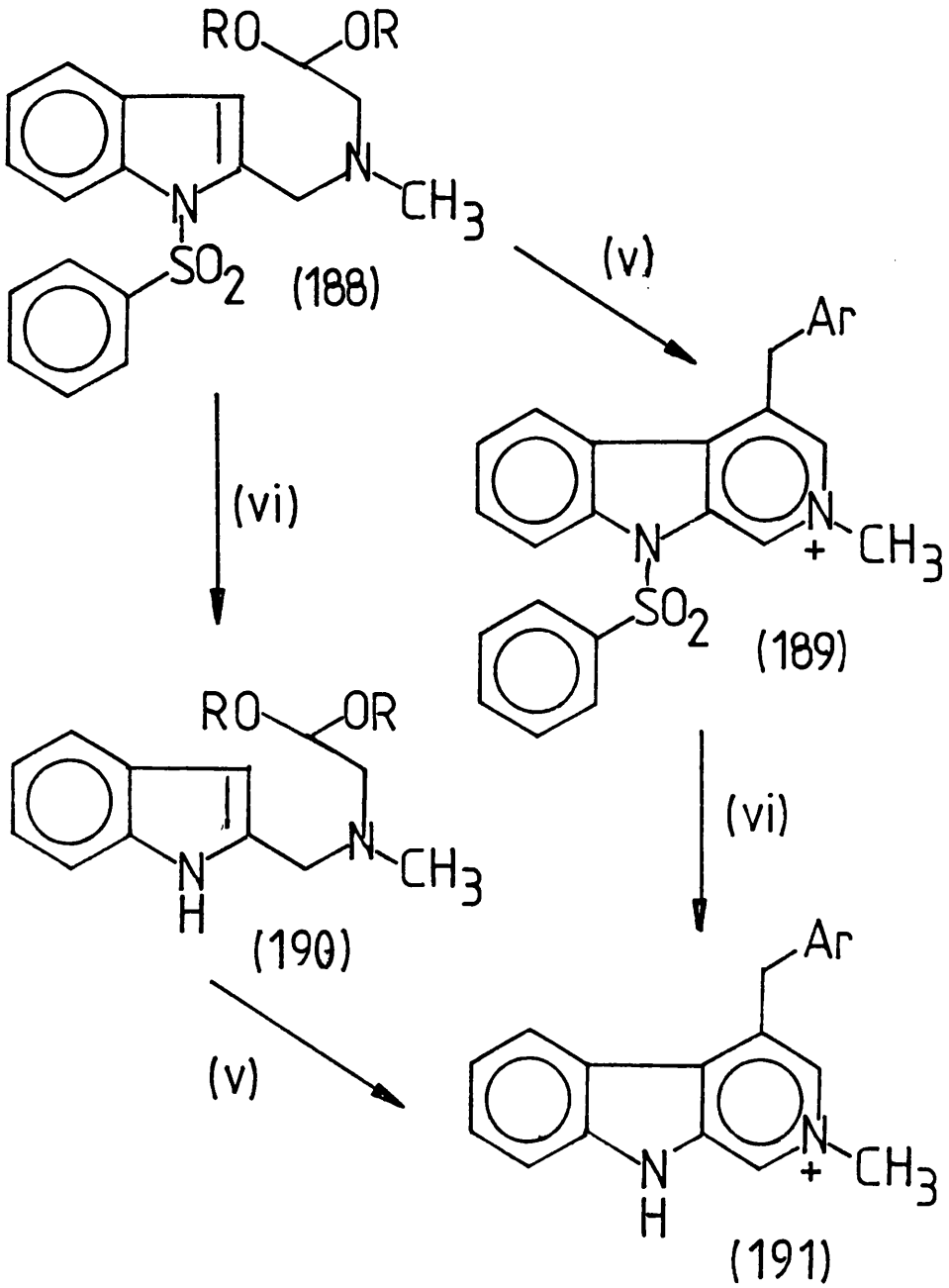
(i) $C_6H_5SO_2Cl$, NaH, Tetrahydrofuran

(ii) See text

(iii) $(RO)_2CHCH_2NH_2$, Toluene, H^+ then $NaBH_4$, Ethanol

(iv) NaH, CH_3I, Tetrahydrofuran

Scheme 23.



(v) ArCHO, H^+

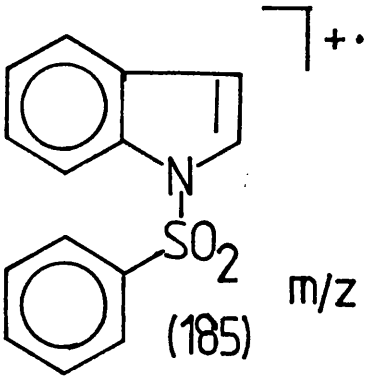
(vi) NaOH, H_2O, Methanol

in the literature. The mass spectrum (not reported in the literature) was typical of an N-substituted indole.[207,208] The relatively strong parent ion occurred at m/z 257 and the base peak was the indole cation (I92, m/z II6) formed by loss of a benzenesulphonyl radical. The relatively strong peak at m/z I4I shows that the loss of an indole radical is also quite a favoured fragmentation. There were the expected peaks at m/z 89 ($C_7H_5^+$) and m/z 77 (phenyl cation). This fragmentation process is outlined in Scheme 24.

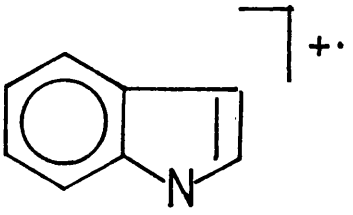
Thus formed the I-benzenesulphonylindole (I85) was subjected to lithiation. The literature procedure utilised tert-butyllithium in tetrahydrofuran but the more readily available n-butyllithium was chosen for convenience in the first instance. Treatment of (I85) with n-butyllithium in tetrahydrofuran at -25°C afforded the reported[I77] deep red solution which was reacted with N-formyl-N-methyl-aniline according to the procedure outlined for I-methoxy-methylindole. Work up of the reaction gave a pale yellow solution which rapidly darkened and yielded a cherry-red oil which afforded crystals of starting material on trituration with ether-hexane. The nature of the red oil was never ascertained, but its colour suggests it may be some sort of isatin derivative (I94) possibly obtained by oxidation of a 2,3-dilithio- derivative.

Several attempts were made to repeat this reaction

Scheme 24.

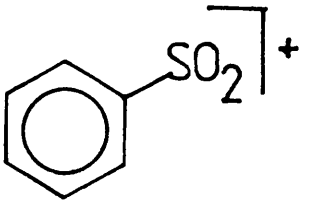


(185) m/z 257



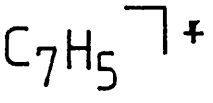
(192)

m/z 116

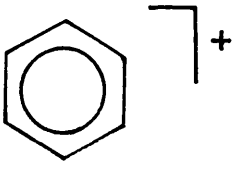


193

m/z 141



m/z 89



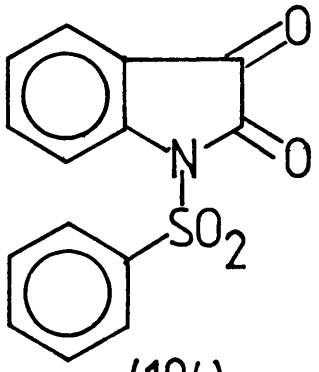
m/z 77

at varying temperatures (-75°C to room temperature), in a different solvent (ether) and using a different carbonyl species (dimethylformamide) and in all cases none of the required product was obtained; only varying proportions of the red oil and starting material being isolated. The reactions were repeated using tert-butyllithium with the same unsatisfactory results.

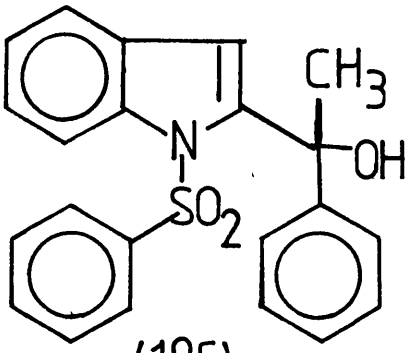
The change in colour on addition of n-butyllithium or tert-butyllithium to a solution of (I85) suggested that lithiation was occurring. Addition of acetophenone to this red solution led to the isolation of the expected I-(I-benzenesulphonylindol-2-yl)-I-phenylethanol (I95), identical to the reported compound.[I77] Thus lithiation was occurring. Whether or not the failure to obtain the required product was due to failure of the 2-lithio-species to react with the carbonyl containing reagent or instabilty of the product was never ascertained as the use of lithium diisopropylamide, as base, solved the problem.

Treatment of a solution of diisopropylamine in tetrahydrofuran at -75°C with n-butyllithium, followed by the addition of I-benzenesulphonyl indole afforded a red solution. Reaction with dimethylformamide yielded on work up an orange oil, after chromatography, in 45% yield. The infra-red and ^{I}HNMR spectra (Appendix I, spectra 9 and I0) appeared consistent with the structure of I-benzene-sulphonylindole-2-carboxaldehyde (I86), but the micro-

analytical value was slightly incorrect (I% out on carbon). Further chromatography failed to improve the analysis and the purity never exceeded 98% (GLC).



(194)

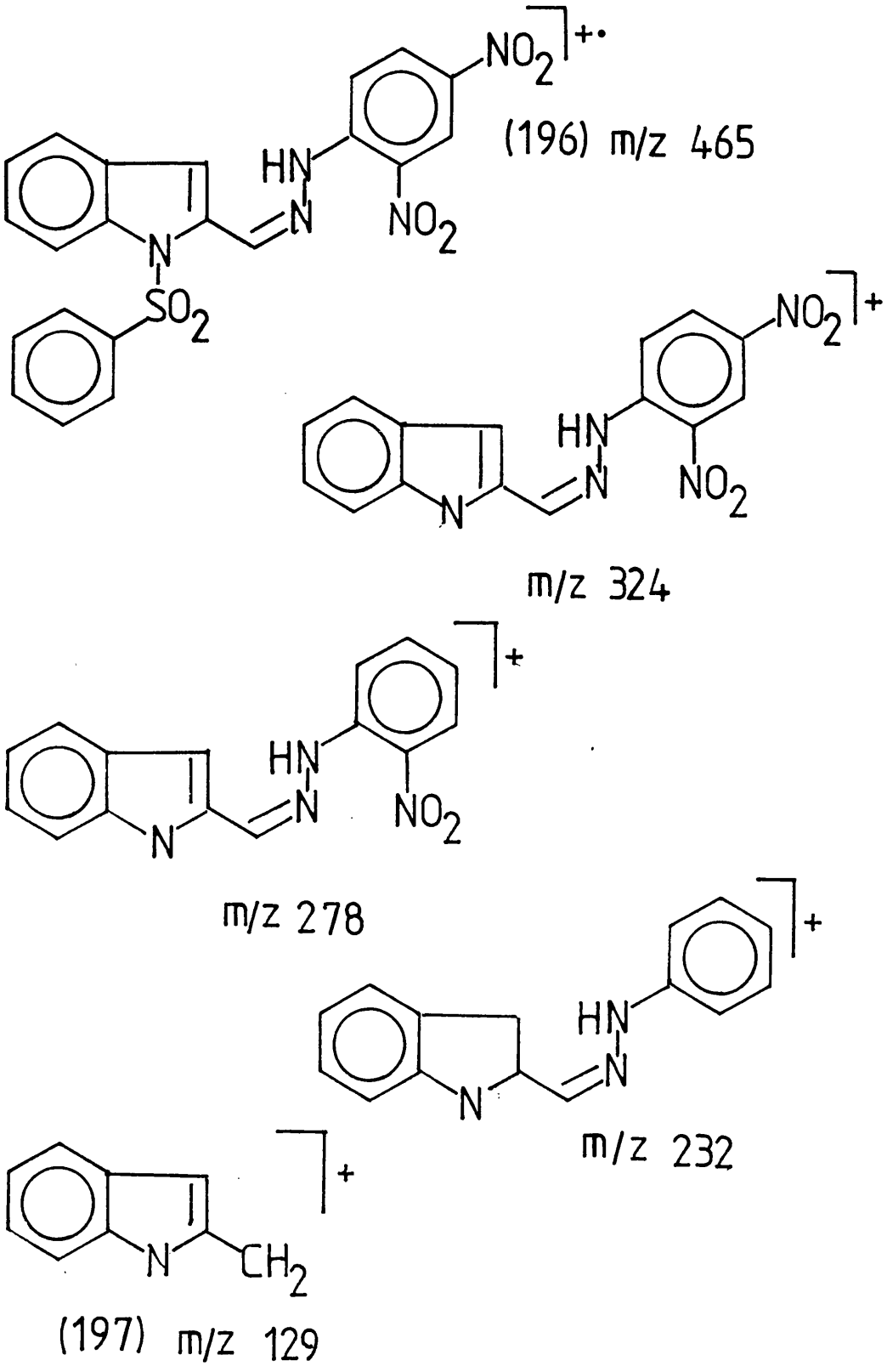


(195)

The 2,4-dinitrophenylhydrazone (I96) was obtained as an orange solid with a melting point of 2I8-20°C. Once again the microanalsis was not satisfactory, even after numerous recrystallisations from glacial acetic acid. The mass spectrum of this compound (Appendix I, spectrum II) was consistent with the required structure and the fragmentation pattern was similar to that of indole-3-carboxaldehyde 2,4-dinitrophenylhydrazone.[208]

There were (Scheme 25) a weak molecular ion at m/z 465 and weak peaks at m/z 324, 278 and 232 corresponding to the loss of a benzenesulphonyl radical and two nitrogen dioxide molecules. The more abundant ions were at m/z I29 corresponding to the indole species (I97) and at m/z 77 (base peak) attributable to the phenyl cation. There were other peaks, such as that at m/z I03, characteristic of an indole system. This supplied sufficient evidence to

Scheme 25.


NO2
+·
(196) m/z 465
HN
N
NO2
N
SO2
NO2
+
HN
N
NO2
N
m/z 324
+
HN
N
NO2
N
m/z 278
+
HN
N
N
m/z 232
+
N
CH2
(197) m/z 129

to confirm that I-benzenesulphonylindole-2-carboxaldehyde (I86) had been formed.

A paper published subsequent to the work described in this thesis[209] reported the preparation of (I86) using lithium diisopropylamide in tetrahydrofuran at -II0°C; the product being a solid, melting point III°C, obtained in 50% yield. The spectra were identical with those obtained by the author. The procedures outlined in this paper[209] were extremely involved and unduly complicated but the yield was no better than that obtained by the simpler procedure described in this thesis. The failure to obtain the compound (I86) as a crystalline product seemed to have no effect on the outcome of subsequent reactions.

The aldehyde (I86) was condensed with amino-acetaldehyde diethylacetal in refluxing toluene in the presence of p-toluenesulphonic acid. The resulting imino-compound was reduced, without purification, with a solution of sodium borohydride in ethanol. The product, N-(2,2-diethoxyethyl)-(I-benzenesulphonyl)-2-indolylmethylamine (I87, R = C_2H_5), was obtained in 30% yield together with a considerable amount of the starting aldehyde. The infra-red and ^{1}HNMR spectra of this previously unrecorded compound (Appendix I, spectra I2 and I3) were entirely consistent with those expected for the amine, and the microanalysis was correct.

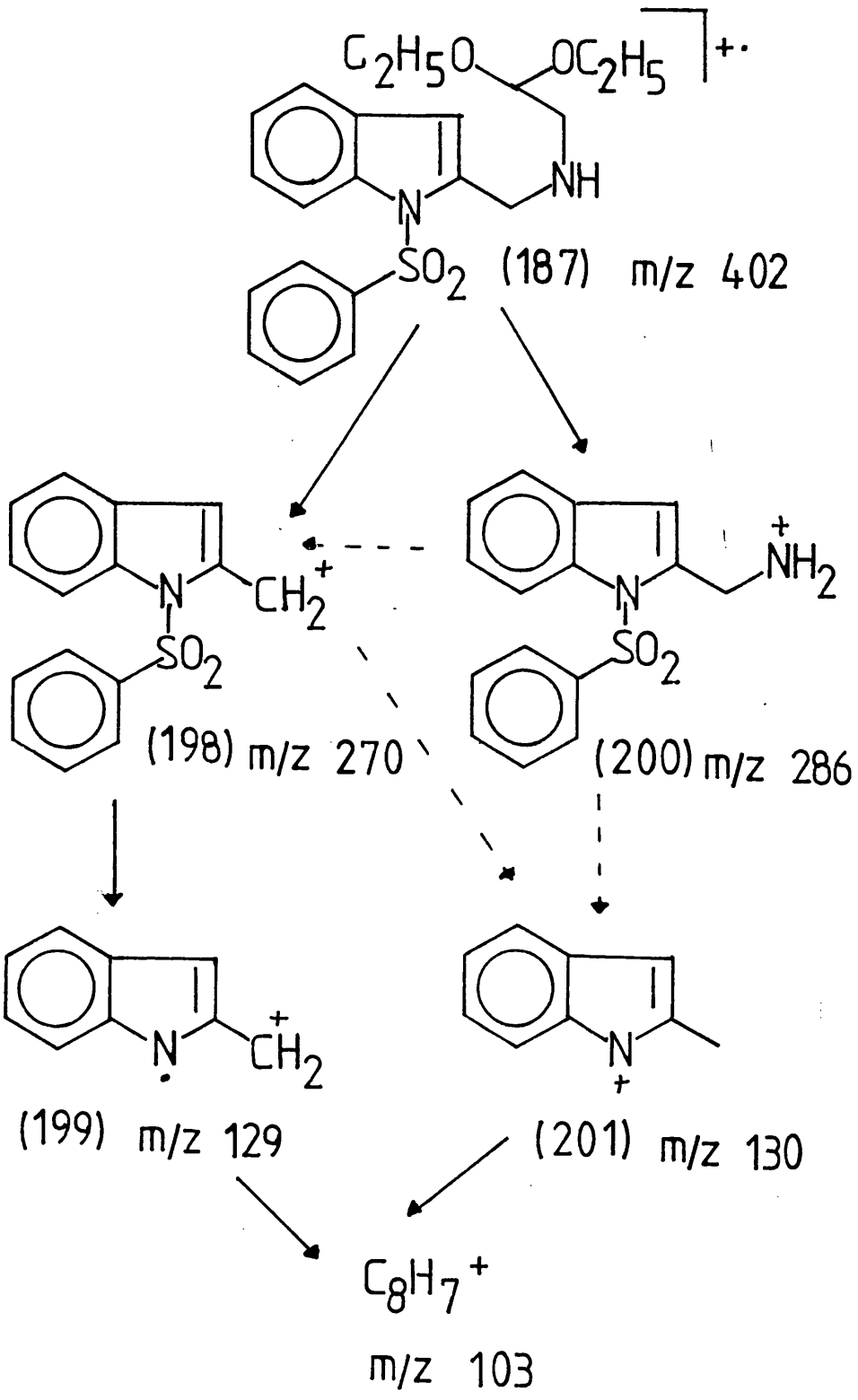
The mass spectrum (Appendix I, spectrum I4) showed an extremely weak parent ion at m/z 402. The major fragmentation route which is outlined in Scheme 26, consisted of cleavage about the secondary amino nitrogen atom. Loss of the diethoxyethylamino radical formed the ion (I98) at m/z 270, which in turn lost a benzenesulphonyl radical to form the ion at m/z I29. This accounted for the larger than expected M+I peak corresponding to the ion at m/z I29.

The ions (I99) and (20I) lost hydrogen cyanide or cyanide radical to form the $C_8H_7^+$ species at m/z I03, which was the base peak, and this fragmented in the usual indole pattern.[207]

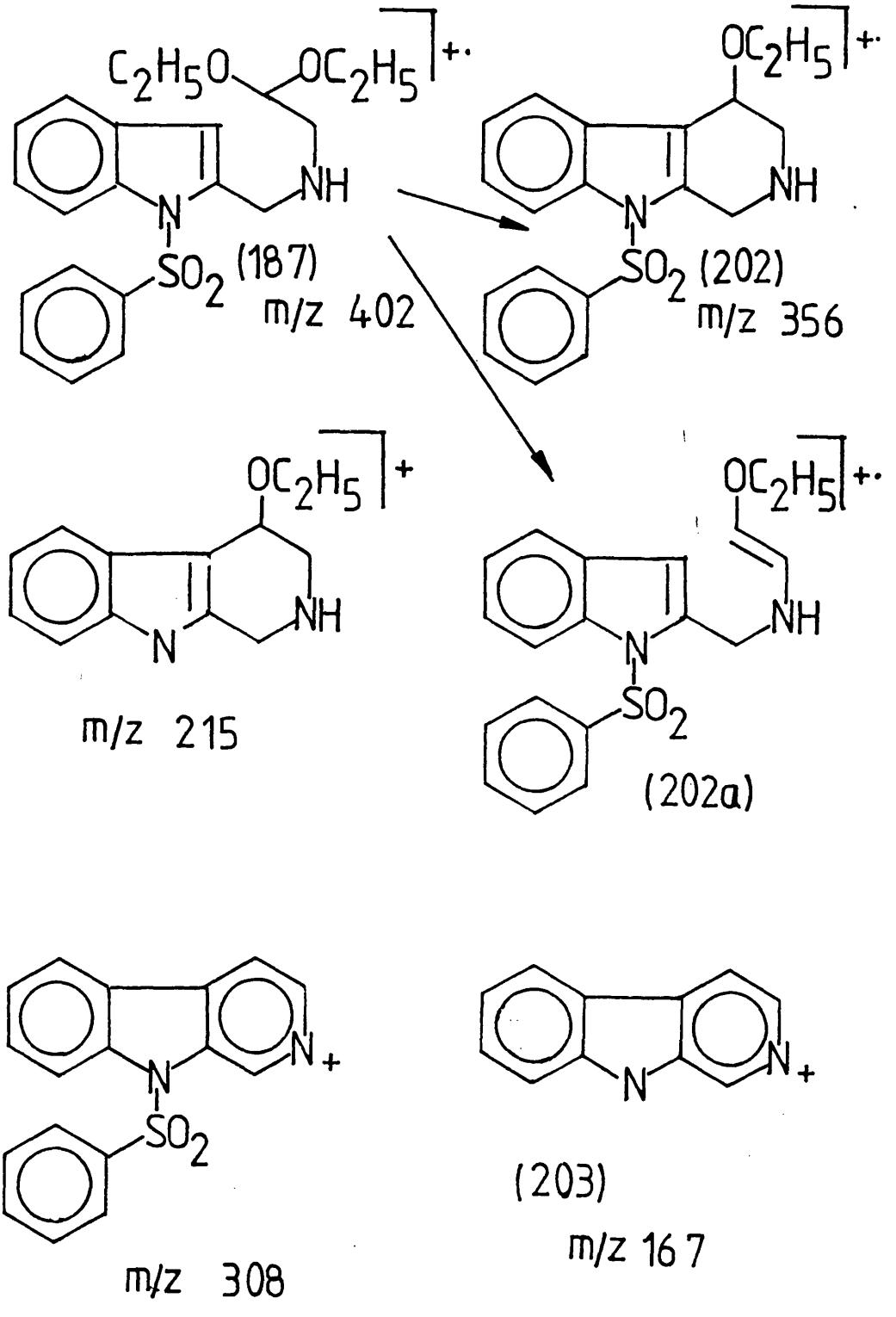
There was an alternative minor fragmentation route outlined in Scheme 27. The parent ion eliminated ethanol and either ring closed to form the tetrahydro-β-carboline species (202) or formed the enolether species (202a), both giving ions at m/z 356. One or both of these ions could then have fragmented as shown in the scheme to form the β-carbolinium species (203) at m/z I67. The ions in this scheme would probably have fragmented to give some of the ions shown in Scheme 26. This indication, however tentative, that the aminoacetaldehyde acetal (I87, R = C_2H_5) could be made to cyclise to a carboline was encouraging.

Compound (I87, R = C_2H_5) was methylated by treatment

Scheme 26.


C2H5O
OC2H5
+·
NH
N
SO2
(187) m/z 402
CH2
+
NH2
(198) m/z 270
(200) m/z 286
(199) m/z 129
(201) m/z 130
C8H7+
m/z 103

Scheme 27.

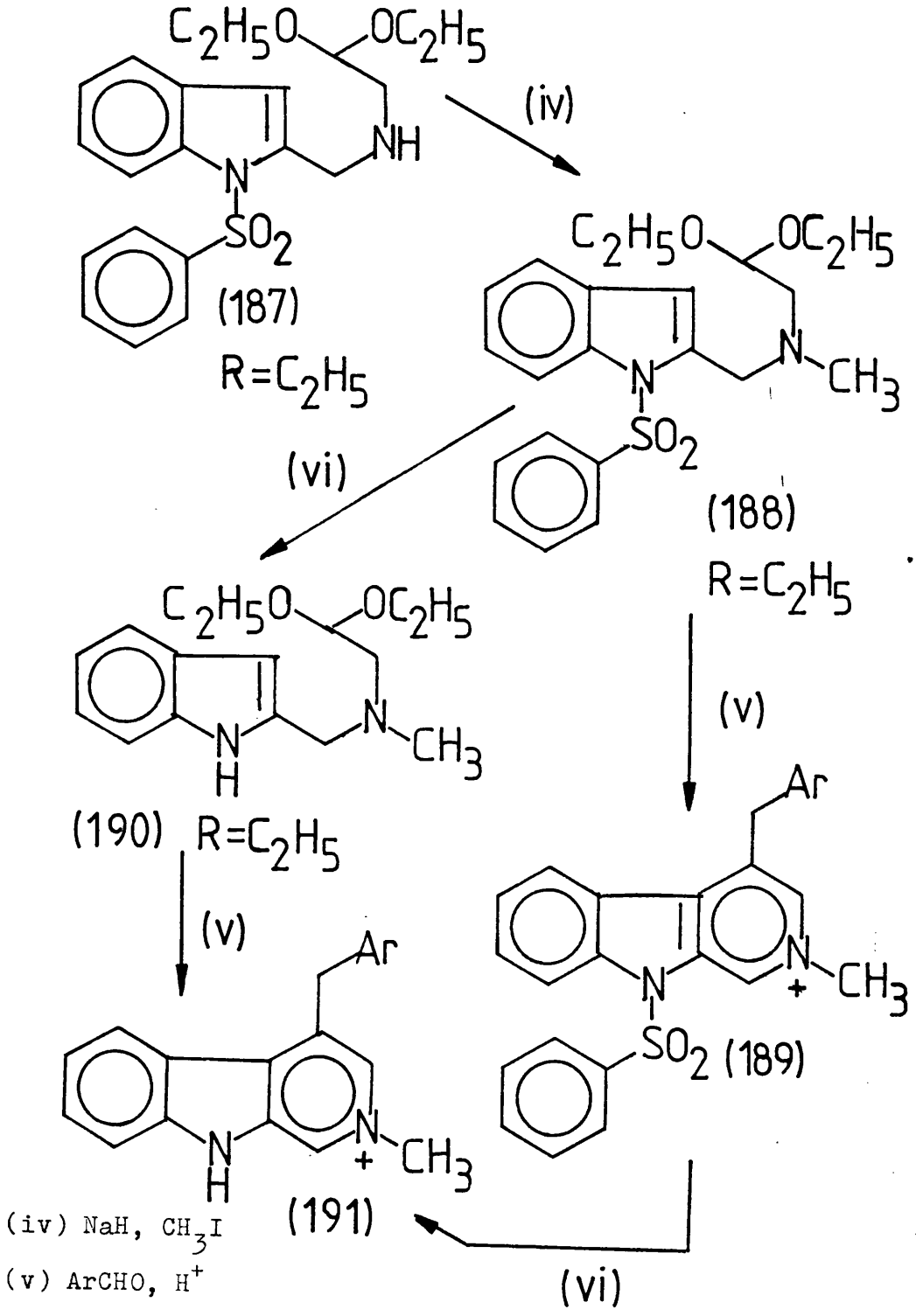

C2H5O
OC2H5
+·
NH
N
SO2
(187)
m/z 402
OC2H5
+·
NH
N
SO2
(202)
m/z 356
OC2H5
+
NH
N
m/z 215
OC2H5
+·
NH
N
SO2
(202a)
N+
N
SO2
m/z 308
N+
N
(203)
m/z 167

with sodium hydride in dioxane followed by the addition of iodomethane. The product (I88, R = C_2H_5), obtained as a red oil in 84% yield after column chromatography, had spectral characteristics entirely consistent with the structure (Appendix I, spectra I5 and I6) and a correct microanalysis.

It was decided to attempt the cyclisation of this compound in the presence of 3-nitrobenzaldehyde under the conditions previously used in the isoquinoline series.[I] The acetal (I88, R = C_2H_5) was treated with 6M hydrochloric acid and left overnight at room temperature to form the 4-hydroxy- compound (204), which was then heated in the presence of the aromatic aldehyde.[I92] Unfortunately the product from the reaction was an oil which was shown not to be the required product (I89, Ar = 3-$NO_2C_6H_4$). This oil afforded an amorphous brown solid after treatment with perchloric acid but the product had an extremely indistinct melting point and gave very poorly resolved spectra. Attempted recrystallisation was not successful in effecting purification, and the microanalytical results were inconsistent.

The reaction was repeated with several other aromatic aldehydes but on each occassion no discrete crystalline product was obtained. Many various sets of experimental conditions were tried; for example the initial induction period was eliminated and longer periods of heating were

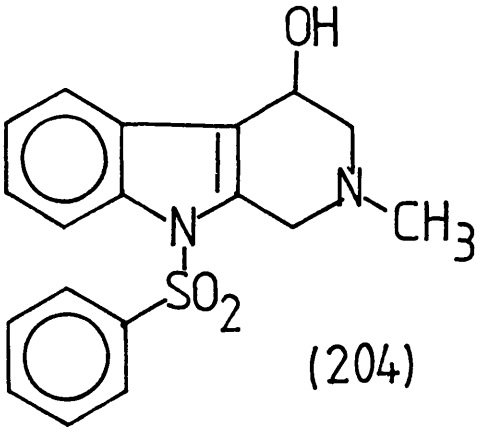
Part of Scheme 23.



(iv) NaH, CH_3I

(v) ArCHO, H^+

(vi) NaOH, H_2O, CH_3OH



(204)

tried, and different acids were employed - all to no avail. We concluded that the benzenesulphonyl group was too deactivating for consideration as a protecting group, and this approach was abandoned.

Accordingly it was decided to use the 2-alkylindole (I90, R = C_2H_5) in cyclisation reactions. This compound was obtained by deprotection of the N-sulphonyl derivative by treatment of it with sodium hydroxide in a mixture of methanol and water.[I77] This procedure gave the requred product in 9I.5% yield; the compound having the expected spectral characteristics (Appendix I, spectra I7 and I8) and a correct microanalysis.

A number of attempts to cyclise the acetal (I90, R = C_2H_5) in the presence of 3-nitrobenzaldehyde failed to yield the corresponding substituted β-carboline. Aqueous hydrochloric acid, acetic acid, perchloric acid and boron trifluoride etherate were ineffective reagents, but the use of aqueous tetrafluoroboric acid met with

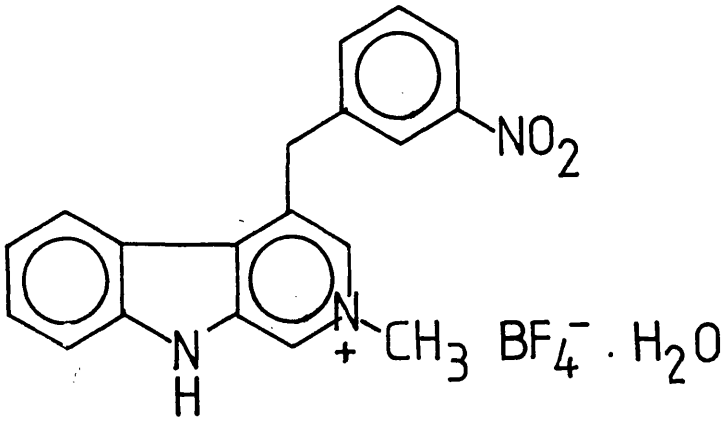
success.

When a mixture of (I90, R = C_2H_5) and 3-nitrobenzaldehyde in ethanol were heated together in the presence of 40% aqueous tetrafluoroboric acid, a brown semi-solid was obtained, which gave yellow crystals on crystallisation from ethanol (2I% yield). The infra-red and ^{1}HNMR spectra (Appendix I, spectra I9 and 20) were consistent with the structure (I9I, Ar = 3-$NO_2C_6H_4$), as its monohydrate, and the microanalysis confirmed this.

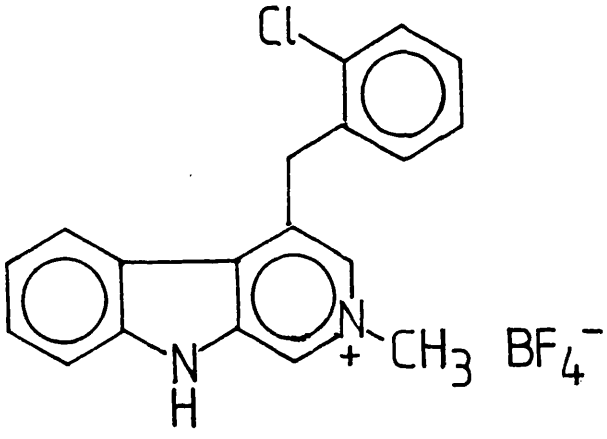
Repetition of the procedure with 2-chlorobenzaldehyde also yielded a solid, but only in II% yield. The ^{1}HNMR and infra-red spectra were in accord with the desired structure (Appendix I, spectra 2I and 22), and the microanalysis was correct for (I9I, Ar = 2-ClC_6H_4). Sadly attempts to repeat the reaction using piperonal and 4-methylbenzaldehyde failed to afford any of the desired products.

The yields of the final products were low but they were not optimised and could be improved, thus it is clear that given a reactive aldehyde the cyclisation - alkylation technique does provide a route to certain 4-substituted β-carboline derivatives.

In order to investigate the reaction further and prepare more derivatives, it was necessary to overcome the difficulties encountered in the preparation of I-benzenesulphonylindole-2-carboxaldehyde and thus provide a larger supply of the acetal (I90). The fact



(191, Ar=3-$NO_2C_6H_4$)



(191, Ar=3-$NO_2C_6H_4$)

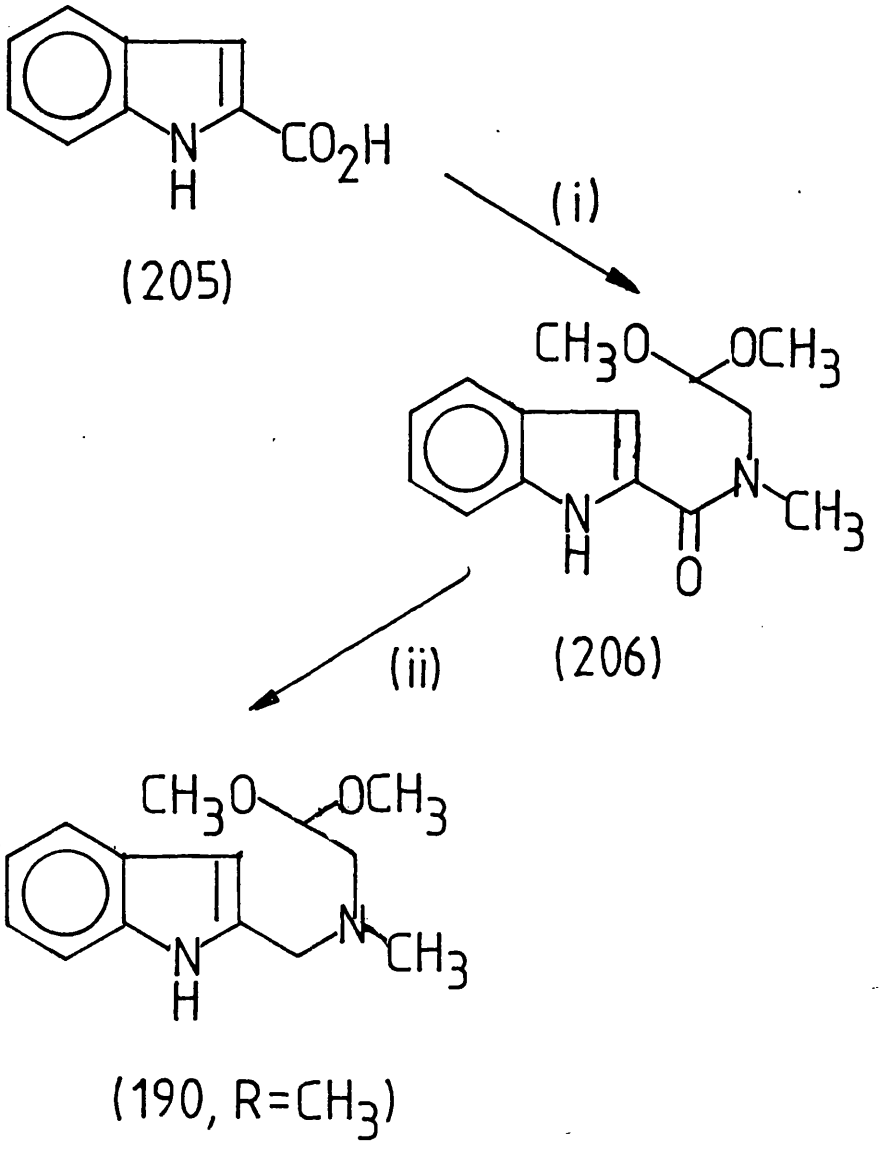
that the presence of the benzenesulphonyl protecting group was not necessary for the cyclisation of the acetal (I90), led to the devising of a new approach to (I90) outlined in Scheme 28.

The method initially chosen for the synthesis of indole-2-carboxylic acid (205) was from 2-nitrotoluene (207);[210,211] which was reacted with sodium ethoxide and dimethyl oxalate to give 2-nitrophenylpyruvic acid (208) in moderate yield. This was cyclised (Scheme 29), with a mixture of iron (II) sulphate and concentrated ammonia, to afford the required acid (205) in low yield. The low yield was due largely to absorption of the product on the iron (III) oxide formed as a by-product of the reaction. The spectral characteristics of (205) and (208) were consistent with the structures, and the melting points agreed with the literature values.[210,211]

In order to circumvent this low yielding procedure, an alternative route was attempted, which is also shown in Scheme 29.[210] Ethyl pyruvate was condensed with phenylhydrazine to give the phenylhydrazone (210); the catalyst used being hydrogen chloride in ethanol, although other acidshave been tried.[210] The product identity was confirmed by spectroscopy and its melting point.

Attempted Fischer indolisation, to form ethyl indole-2-carboxylate (209), failed when alcoholic hydrogen chloride was used as the catalyst. Similarly , alcoholic sulphuric

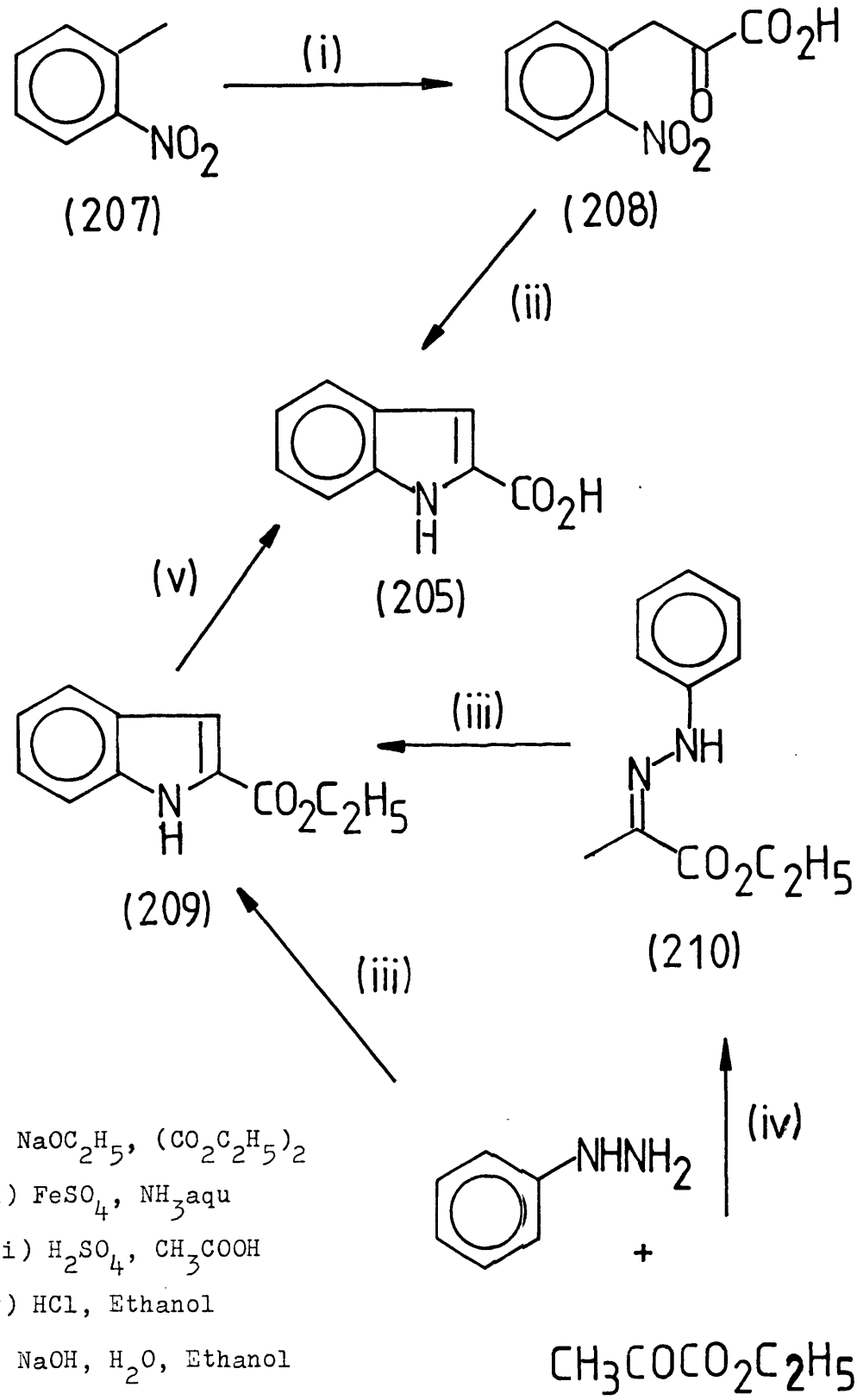
Scheme 28.



(i) $SOCl_2$, Toluene then $(CH_3O)_2CHCH_2NHCH_3$

(ii) $LiAlH_4$, Tetrahydrofuran

Scheme 29.



(i) $NaOC_2H_5$, $(CO_2C_2H_5)_2$

(ii) $FeSO_4$, NH_3aqu

(iii) H_2SO_4, CH_3COOH

(iv) HCl, Ethanol

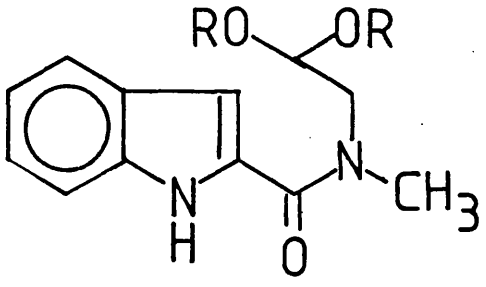
(v) NaOH, H_2O, Ethanol

acid, aqueous sulphuric acid, zinc chloride in ethanol or hydrogen bromide in acetic acid were equally unproductive, but the use of concentrated sulphuric acid in glacial acetic acid[210,211] effected the cyclisation in reasonable yield.

It was found, after some investigation, that ethyl indole-2-carboxylate (209) could be prepared on a large scale and with an improved yield, by reacting ethyl pyruvate with phenylhydrazine or phenylhydrazine hydrochloride in a concentrated sulphuric acid - glacial acetic acid mixture, the intermediate hydrazone (210) not being isolated.

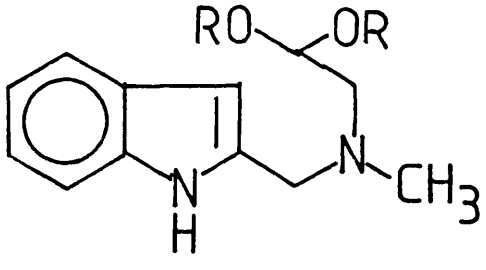
The ester was hydrolysed to indole-2-carboxylic acid (205) by boiling with aqueous-ethanolic sodium carbonate solution,[210,211] and converted into the corresponding acid chloride by heating with thionyl chloride in toluene. This was reacted, without purification, with N-methylaminoacetaldehyde dimethylacetal to give, on work up, an 84% yield of N-(2,2-dimethoxyethyl)-N-methyl-indole-2-carboxamide (206). This is a new compound, although its diethyl equivalent (211) is known.[210,211]

This product was reduced with lithium aluminium hydride in tetrahydrofuran to produce N-(2,2-dimethoxyethyl)-N-methyl-2-indolymethylamine (190, R = CH_3) in good yield. The spectral characteristics (Appendix I, spectra 23 and 24) corresponded to those expected for



R = CH_3 (206)

R = C_2H_5 (211)



(190) R = CH_3, C_2H_5

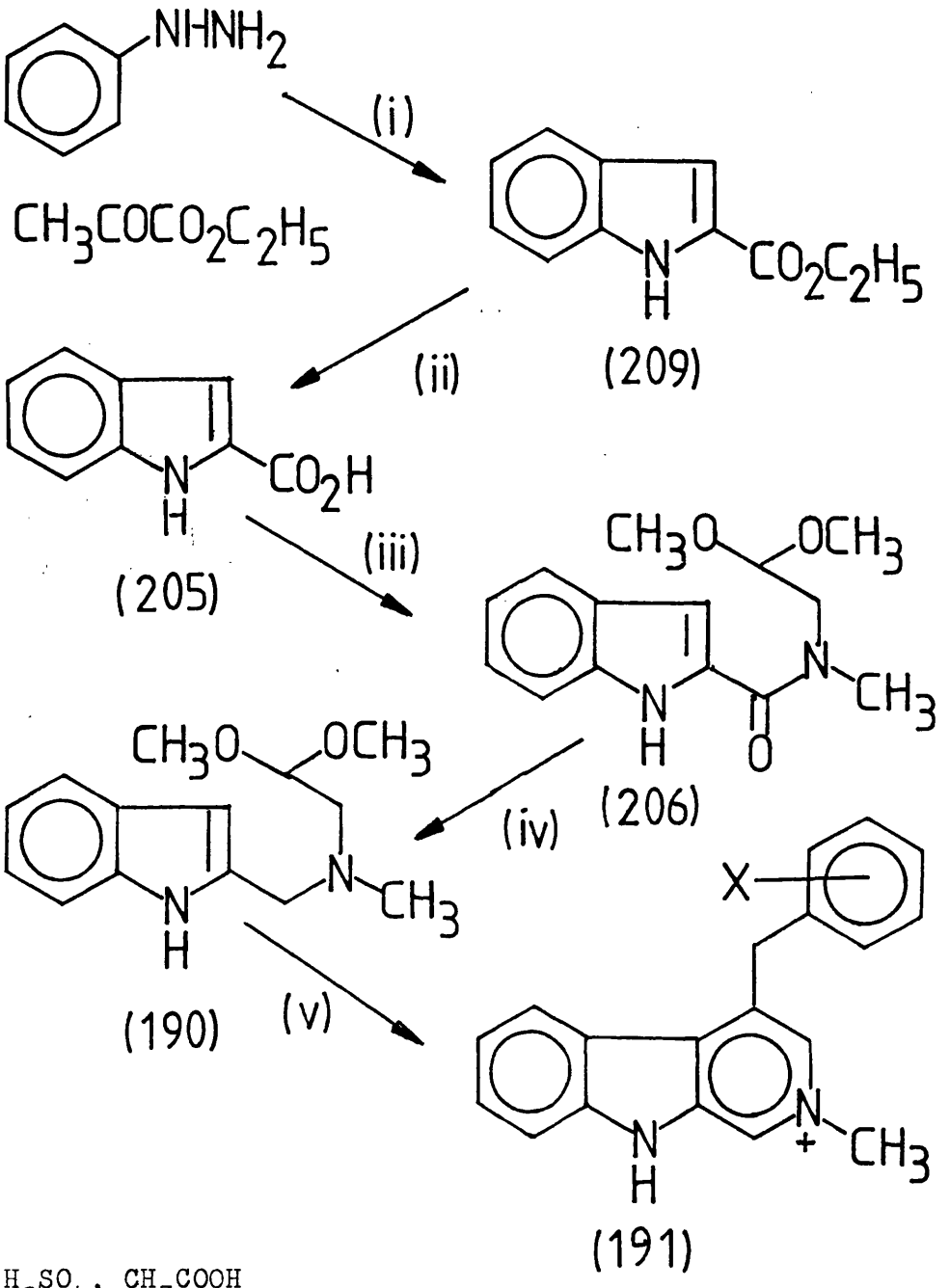
the structure and were comparable to those of (I90, R = C_2H_5), obtained by hydrolysis of the I-benzenesulphonyl compound (I88, R = C_2H_5).

The overall procedure, which is summarised in Scheme 30, was much better in terms of yield and ease of reaction than the route illustrated in Scheme 23. Hence, with suitable improvement in the yield of the final cyclisation step, the synthesis would provide a very flexible route to 4-substituted-β-carbolinium salts. The slightly inferior scheme, based on I-benzenesulphonylindole-2-carboxaldehyde, would, however, be useful if the benzene ring in (I9I) needed to carry substituents susceptible to reduction by lithium aluminium hydride (see Scheme 30).

Unfortunately, due to lack of time, it was not possible to attempt any further cyclisations of the acetal (I90) with other aldehydes, and hence it is not yet possible to specify the range of aldehydes which will undergo this reaction. This requires further investigation. Another area which requires investigation, is the range of substituents which can be placed in the benzene ring of the acetal (I90) without affecting the reactivity and ease of cyclisation.

In conclusion, the work described in this thesis has developed a potentially viable method for the synthesis of 4-substituted-β-carbolines, and further work will easily provide a range of molecules for biological testing.

Scheme 30.



(i) H_2SO_4, CH_3COOH

(ii) Na_2CO_3, H_2O, Ethanol

(iii) $SOCl_2$, Toluene then $(CH_3O)_2CHCH_2NHCH_3$

(iv) $LiAlH_4$, Tetrahydrofuran.

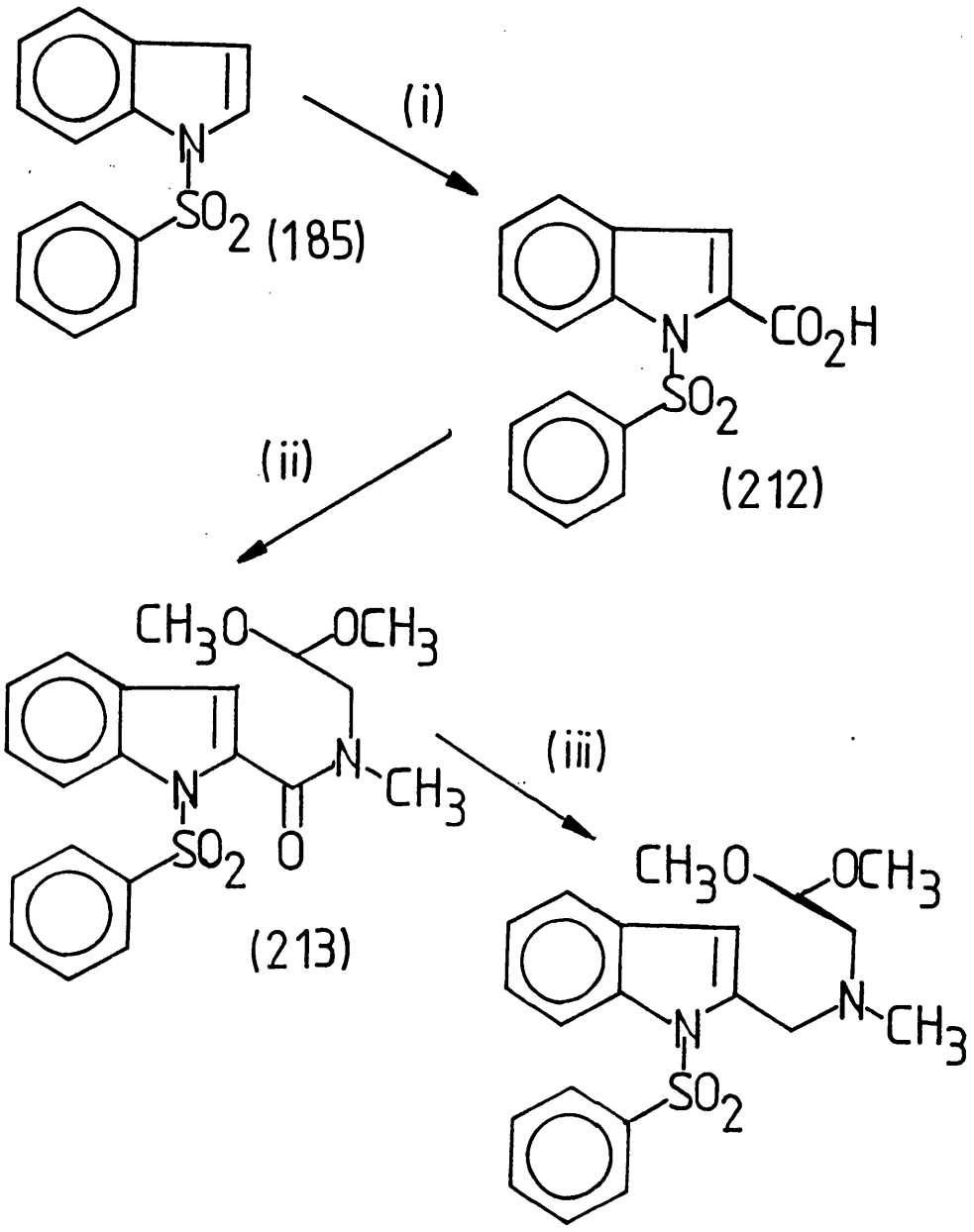
(v) ArCHO, HBF_4, Ethanol

Before the synthetic scheme outlined in Scheme 30 was devised and before the presence of the benzenesulphonyl protecting group was deemed unnecessary, another synthetic route was considered. This is outlined in Scheme 31. I-Benzenesulphonylindole (185) was reacted with butyllithium in tetrahydrofuran, according to the literature procedure,[177] to afford I-benzenesulphonylindole-2-carboxylic acid (212) in 51% yield. The product had infra-red and ^{1}HNMR spectra and a melting point comparable with that quoted in the literature.[177] The fragmentation pattern of the mass spectrum, outlined in Scheme 32, was entirly consistent with that expected for a substituted indole.[207,208]

The acid reacted with thionyl chloride in boiling toluene, followed by the addition of N-methyl-aminoacetaldehyde dimethylacetal, to yield I-benzenesulphonyl-2-(N-(2,2-dimethoxyethyl)-N-methyl)-carboxamide (213) in 70% yield. This previously unrecorded compound, an orange oil, had an infra-red and ^{1}HNMR spectrum (Appendix I, spectra 25 and 26) which fully supported the required structural assignment.

The reduction of (213) to give (188, R = CH_3), using lithium aluminium hydride, was not undertaken due to the decision to abandon work on compounds containing the benzenesulphonyl protecting group, and because of the success in cyclising the acetal (190).

Scheme 3I.

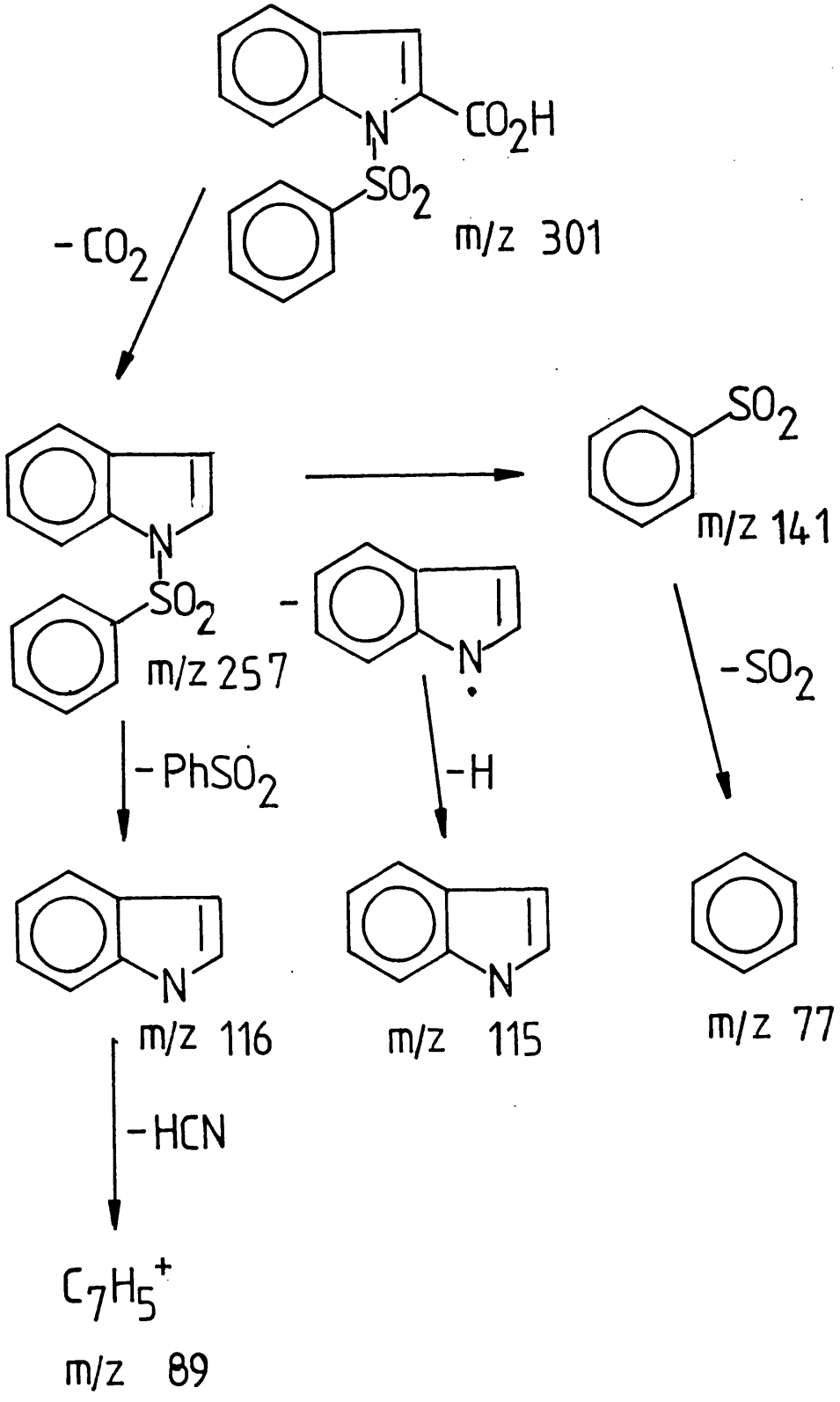


(i) $n\text{-}C_4H_9Li$, CO_2, Tetrahydrofuran

(ii) $SOCl_2$, Toluene then $(CH_3O)_2CHCH_2NHCH_3$

(iii) $LiAlH_4$, Tetrahydrofuran

Scheme 32.

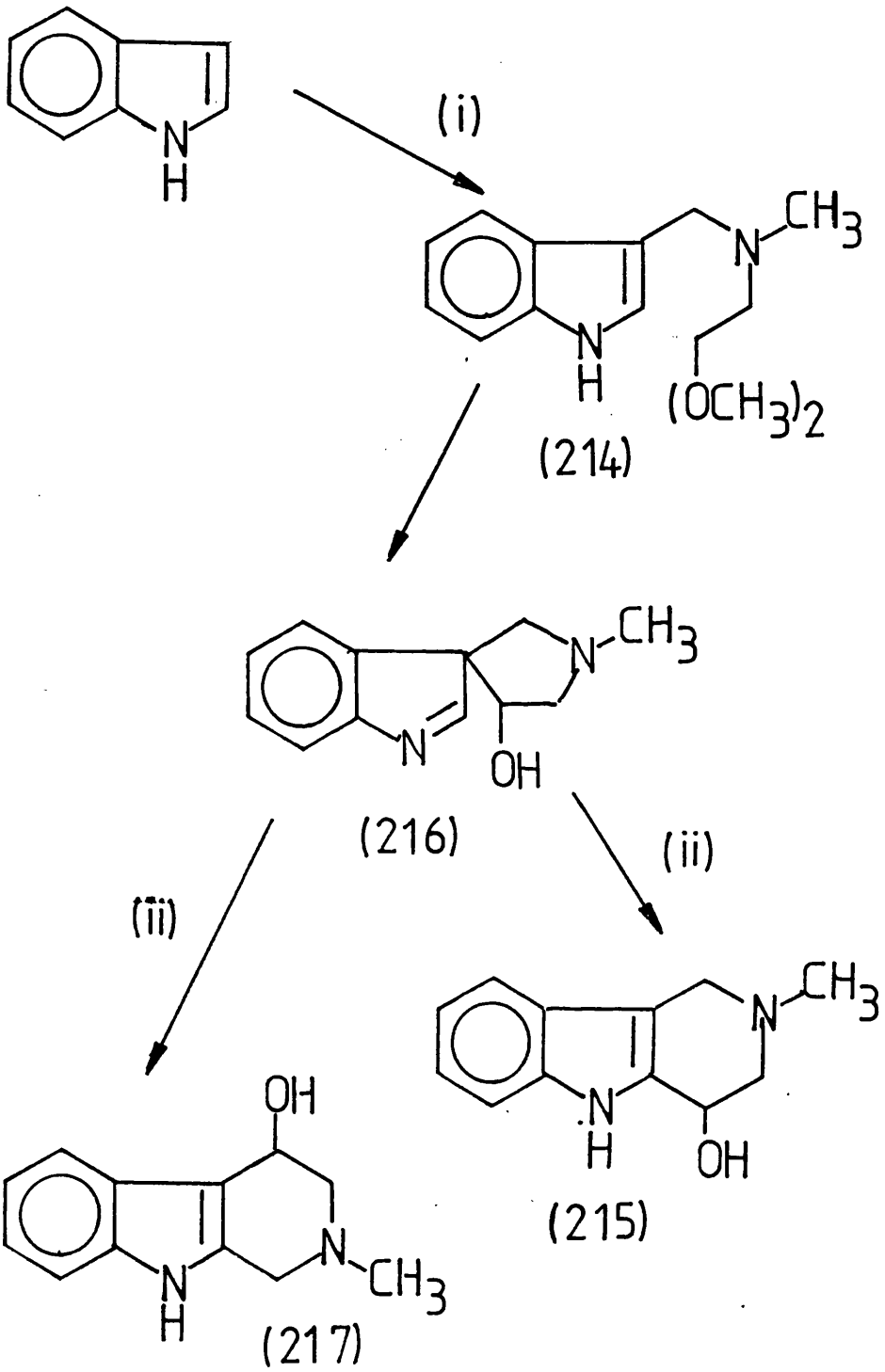

CO2H
N
SO2
m/z 301
-CO2
SO2
m/z 141
-SO2
m/z 257
-PhSO2
-H
m/z 116
m/z 115
m/z 77
-HCN
C7H5+
m/z 89

In a private communication and subsequent publication, Bobbitt et al.[213] described the preparation of the acetal (214) from indole, formaldehyde and N-methylaminoacetaldehyde dimethylacetal, and its cyclisation to 1-hydroxy-1,2,3,4-tetrahydro-γ-carboline (215). In the isoquinoline area these hydroxy derivatives are intermediates in the preparation of the 1,2-dihydro- compounds,[195] and it was decided that (215) could provide a source of 1-substituted-γ-carbolines.

Repetition[214] of the procedures outlined by Bobbitt gave the acetal (214) in 88% yield (Scheme 33). The infrared spectrum and melting point were identical to those described in the literature,[213] the ^{1}HNMR spectrum (not reported in the paper) was entirely consistent with the structure (Appendix I, spectrum 27) and the microanalysis was correct.

This compound was treated with 6M hydrochloric acid, exactly as described by Bobbitt, and a hydroxycarboline derivative obtained in 52% yield. The product had a melting point similar to that reported in the literature and the mass spectrum contained a molecular ion of the correct mass, although it afforded very little extra information. The proton NMR spectrum (Appendix I, spectrum 28), which was not reported in the literature,[213] showed the resonances expected of a hydroxycarboline, but it was not possible to ascertain whether it was the

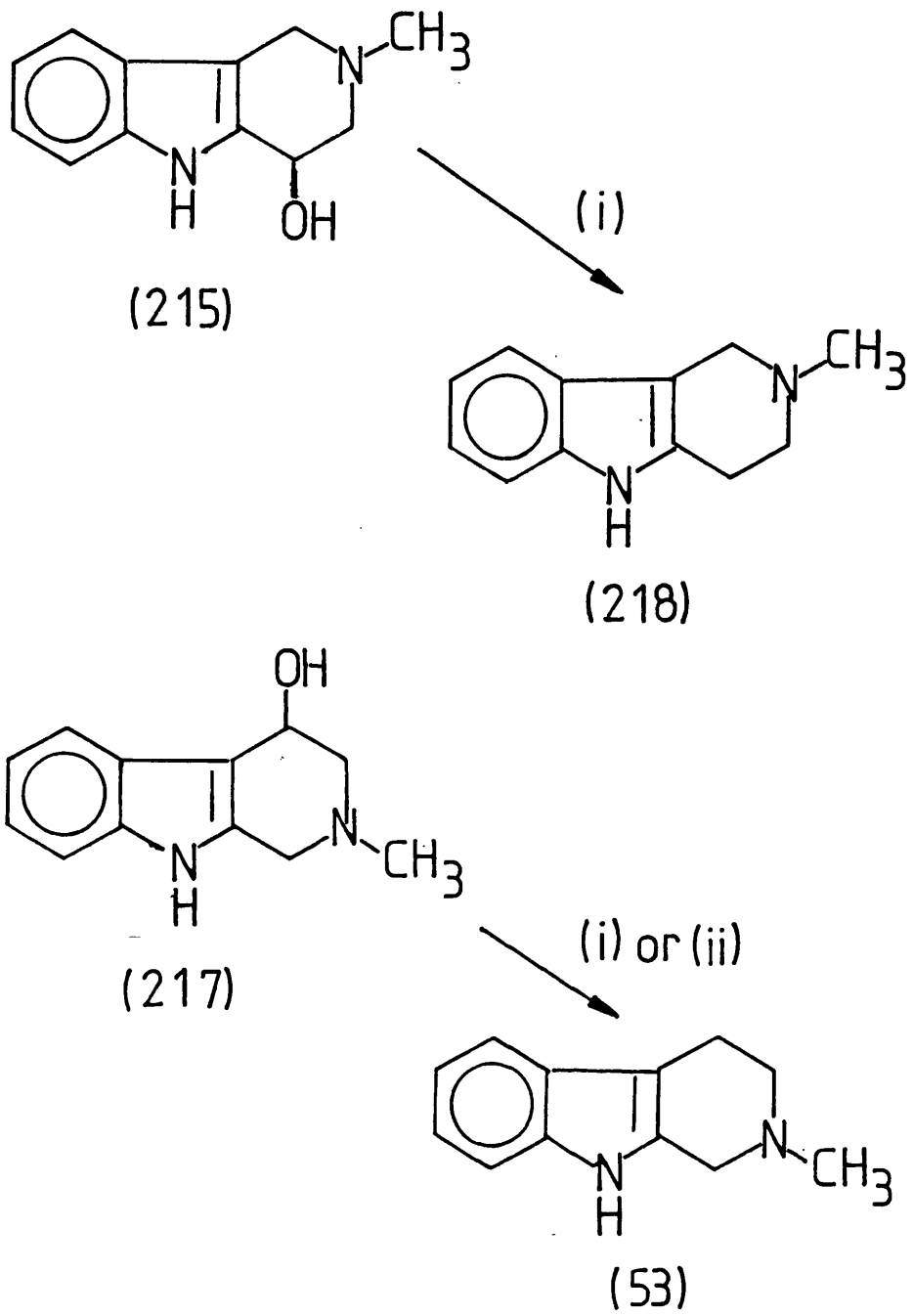
Scheme 33.



(i) $POCl_3$, $CH_3NHCH_2CH(OCH_3)_2$, Dimethylformamide

(ii) H^+, H_2O, Ethanol

Scheme 34.



(i) Pd/C, HCl

(ii) $AlCl_3$, $LiAlH_4$, $(n\text{-}C_4H_9)_2O$

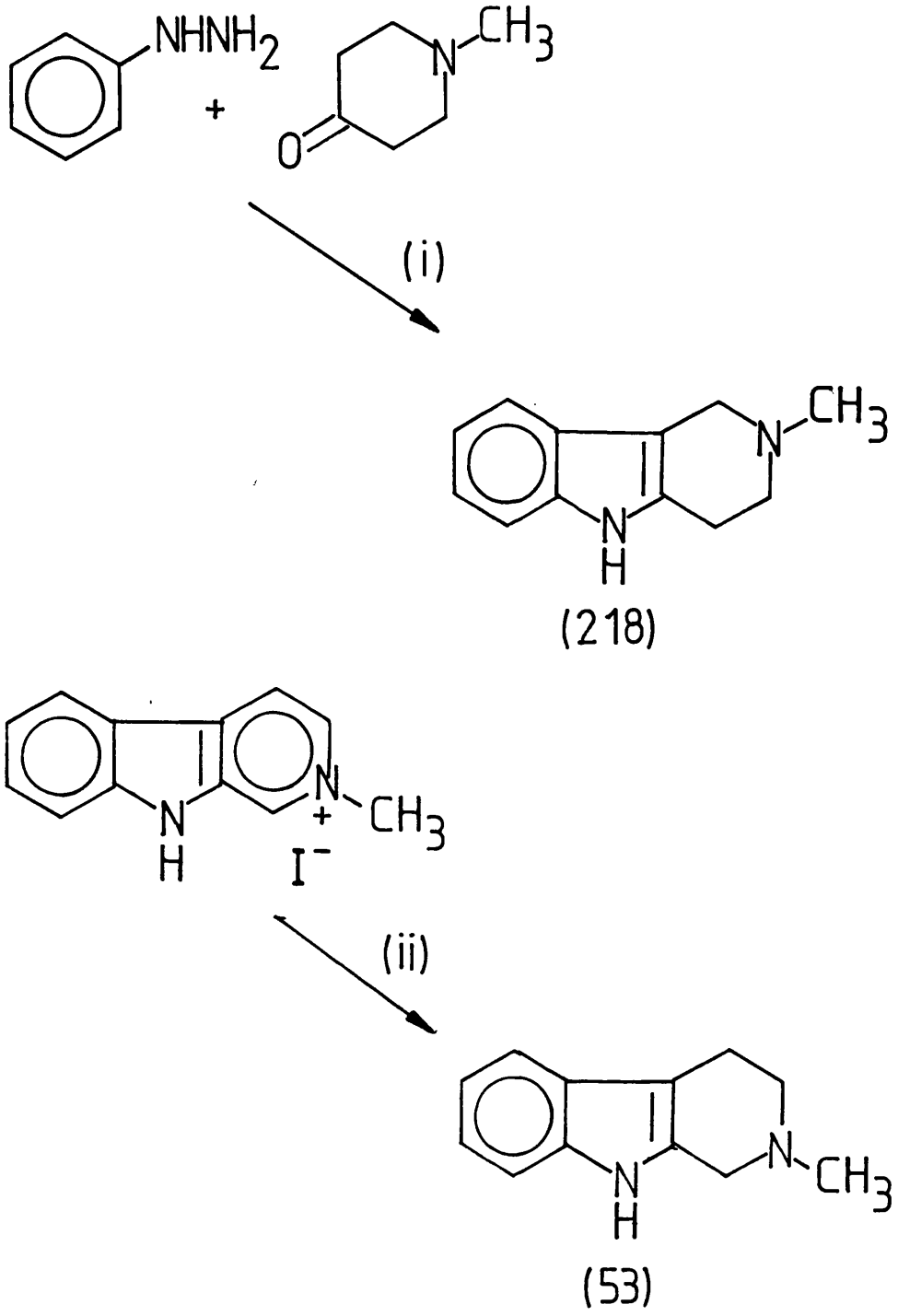
β-carboline derivative (217) or the γ-carboline derivative (215).

The proof supplied by the American chemists for the nature of their carboline derivative, was that it gave 2-methyl-I,2,3,4-tetrahydro-γ-carboline (218) on hydrogenation over palladium on charcoal. The structure of the product was confirmed by its melting point relative to the literature value, although a direct comparison with an authentic specimen was apparently not carried out.

When the hydroxycarboline from our cyclisations[214] was subjected to the same catalytic hydrogenation, the product isolated had a melting point of 215-6°C corresponding to that of 2-methyl-I,2,3,4-tetrahydro-β-carboline (53), rather than the value of 171-2°C correspomding to (218).[116,213] Reduction of the hydroxy-compound with a mixture of lithium aluminium hydride and aluminium chloride[215] also yielded the tetrahydro-β-carboline. This procedure is outlined in Scheme 34.

In order to confirm these results, the tetrahydro-β- and γ-carbolines were prepared by unambiguous routes for comparison (Scheme 35). The γ-carboline (218) was prepared by a Fischer type cyclisation using phehylhydrazine (or its hydrochloride) and N-methyl-4-piperidone,[216] using a method similar to that used for the preparation of ethyl indole-2-carboxylate. 2-Methyl-I,2,3,4-tetrahydro-β-carboline (53) was prepared by the sodium borohydride

Scheme 35.



(i) H_2SO_4, CH_3COOH

(ii) $NaBH_4$, Methanol

reduction of the β-carbolinium salt (I42).

Mixed melting points of the reduction product from the hydroxy compound with these two authentic samples, showed no depression of melting point when mixed with the tetrahydro-β-carboline derivative. The same result was obtained from mixed melting point determinations using the picrate salts.

Electrophilic substitutions on 3-substituted indoles nave been shown[2I7,2I8] to proceed via a spirocyclic indolenine derivative, in this case(2I6). Such an intermediate could be anticipated to rearrange to either the β- or the γ-carboline skeletons ((2I7) and (2I5) respectively), and in our case it was clearly the β-carboline that was formed.

Due to lack of time this work was not carried any further , and consequently the contradiction in results from the two sets of authors[2I3,2I4] has not been explained. One possible explanation for this anomaly is that the cyclisation of the acetal (2I4), via the indolenine (2I6), gives a mixture of (2I5) and (2I7). Differences in experimental techniques and such factors as ambient temperature, may effect the outcome of the cyclisation or cause a different separation of the mixture of products during work up. Any further investigations in this area should concentrate on the application of techniques such as ^{I3}CNMR and HPLC, in order to effect a separation of

the possible mixture of isomers, and to positively confirm their structures.

In conclusion it can be stated that the success in preparing 4-substituted-β-carbolinium salts from the indoleamino acetal (I90), analogous to the isoquinoline chemistry, shows that I,2-dihydro-β-carbolines are intermediates in this type of reaction and are undergoing enamine type reactions. However, the failure to obtain pure products from the partial reduction of the carbolinium salts, suggests that the enamine character is not easy to control or predict.

Any further work in the β-carbolinium field, based on the work in this thesis, should be directed towards the extension of the acetal cyclisations with other aldehydes and with substituted acetals. Further work on the partial reduction of the carbolinium salts may be warrented, particularly in the light of the success of Knabe and Saggau[I90] with their I-substituted-I,2-dihydro-β-carbolines, but it would require a detailed investigation to find suitable substituent groups and nucleophiles, to provide stable intermediates and products.

Finally the work in this thesis, after many setbacks and problems, succeeded in developing a viable method for the synthesis of 4-substituted-β-carbolines and further work will easily provide a range of molecules for biological testing.

EXPERIMENTAL

Melting points, obtained on a Koffler hotstage, are uncorrected and mass spectra were recorded on an AEI MS I2 or a Matt 44 machine. Proton Nuclear Magnetic resonance spectra were recorded on a JEOL PSIOO or Varian EM 360 spectrometer at IOO and 60 MHz respectively. The values are expressed as parts per million downfield from tetramethylsilane as internal standard. Unless stated otherwise in the text, all ultra-violet spectra were recorded in 95% ethanol solution on a Perkin-Elmer 402 spectrophotometer.and infra-red spectra were taken as nujol mulls (solids) or smears (liquids) on a Perkin-Elmer model I97 or 237 or on a Unicam SP200 machine.

I,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid (I4I).

A mixture of dl-tryptophan (IO.0g, 0.049 mole), sodium hydroxide (2.0g, 0.05 mole) and 37% formaldehyde solution (5.6ml, 0.07 mole) in water (500ml) was stirred at 36-40°C for 48 hours. The resulting pale yellow solution was cooled in ice and acidified, to approximately pH 6.5, with glacial acetic acid (4ml). The white precipitate was filtered off and recrystallised from 2M ammonium hydroxide solution to afford I,2,3,4-tetrahydro-β-carboline -3-carboxylic acid (I4I) (5.0g, 47%) as white plates, m.p. 300°C (Lit.,[I60] 306°C); ν_{max} 3440, 3380 cm^{-I} (NH, NH_2^+), I620 cm^{-I} (CO_2^-); δ_H (DMSO-d_6) 9.9 (s, IH), 8.2 (s, 2H), 7.44-6.9 (m, 4H), 5.I (s,2H), 4.6 (t, IH, J=2Hz), 2.46 (d, 2H, J=2Hz).

β-Carboline (7).

(a) Potassium Dichromate Oxidation.

The crude, caustic solution from the synthesis of (I4I) was neutralised with glacial acetic acid (4ml) and diluted to 2500ml with water. The resulting suspension was heated to boiling and treated dropwise with a solution of potassium dichromate (50.0g, 0.I7 mole), in water (500ml) and glacial acetic acid (I00ml), over a period of 45 minutes. The solution darkened, carbon dioxide was evolved and a thick brown precipitate appeared. Boiling was continued for two minutes after the addition was complete, and the mixture cooled and the excess dichromate destroyed by the passage of sulphur dioxide gas through the solution. Sodium carbonate was added to definite alkalinity and the resulting gelatinous mass continuously extracted with ether (I000ml) for 48 hours. Drying of the ether extracts over magnesium sulphate and evaporation under reduced pressure gave a yellow solid. Recrystallisation from methanol yielded (7) (2.4g, 29%) as pale yellow needles, m.p. I98-20I°C (Lit.[I60] I98.5°C; I99-20I°C[I6I]); λ_{max} (ε_{max}) 2I5 nm (8 350), 237 (I7 480), 250 (shd, II 960), 284 (5 350), 29I (8 980), 340 (I I00), 352 (I 260); δ_H ($CDCl_3$-DMSO-d_6) 8.74 (m, IH), 8.04 (m, 3H), 7.53 (m, 2H), 7.I6 (m, 2H), 6.66 (m, IH).

(b) Sodium Hypochlorite Oxidation.

A solution of the acid (I4I) (3.0g, 0.0I4 mole) in

2M sodium hydroxide solution (IOml) was treated with 2M hydrochloric acid dropwise until crystals just appeared. The solution was diluted with water to 200ml and ether was added to the stirred solution, followed by the addition of aqueous sodium hypochlorite solution (60ml, IO% available chlorine). The mixture was stirred at room temperature for two hours, the etherial layer separated and the aqueous layer continuously extracted with ether (IOOOml). The organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to yield a pale yellow solid. Recrystallisation from methanol gave (7) as an off-white solid (I.2g, 50%), m.p. and spectra identical to dichromate oxidation product.

(c) Fremy's Salt Oxidation.

A solution of (I4I) (3.0g, 0.0I4 mole) in 40% sodium carbonate solution (600ml) was treated with Fremy's Salt (8.0g, 0.03 mole), and stirred at room temperature for 48 hours. A TLC of the mixture (chloroform) showed no β-carboline (7) present and many components. Evaporation under reduced pressure afforded a red gum. The reaction was abandoned.

N-Formyl-Tryptophan (I52).

Tryptophan (20.4g, 0.I mole) was dissolved in the minimum quantity of formic acid and treated, with ice

cooling, with acetic anhydride (II.2g, 0.II mole). The solution was stirred at room temperature for three hours and then poured into water (500ml). The resulting white solid was filtered off, dried in air and recrystallised from ethanol-benzene, to yield (I52) (I5.3g, 66%) as white needles, m.p. I65-6°C (Lit.[I72] I67-8°C); λ_{max} (ε_{max}) 227 nm (20 205), 276 (shd, 6 500), 283 (6 850), 29I (5 650); υ_{max} 3400, 3360 cm^{-I} (NH), I7I0, I630 (CO); δ_H (CF_3COOH) 8.I5 (d, IH, J=2Hz), 7.62-6.92 (m, 8H), 5.08 (dd, IH, J=6Hz, 8Hz), 3.45 (d, 2H, J=6Hz); m/z 232 (M^+).

3,4-Dihydro-β-carboline-3-carboxylic Acid (I08).

Polyphosphoric ester (25.0g, large excess) in dry chloroform (I00ml) was added to a suspension of N-formyl-tryptophan (I52) (I5.0g, 0.065 mole) in dry chloroform (250ml). The solution was stirred at room temperature for approximately 24 hours, until the band at 280 nm in the UV of the original solution had been completely replaced by a band at 365 nm. The solution was cooled in ice, treated with cold water (250ml) and stirred for a further two hours. The chloroform was removed by evaporation under reduced pressure and the residual aqueous solution acidified with 70% aqueous perchloric acid and cooled in ice. The resulting solid was filtered off, dried in air and recrystallised from methanol to

yield the perchlorate salt of (I08) (I5.0g, 74%) as yellow needles, m.p. 2I2°C (Lit.[I7I] 2I3-4°C); λ_{max} (ε_{max}) 248 nm (6 720), 365 (I4 000); ν_{max} 3280, 2500 cm^{-I} (NH^+, OH), I740 (CO), I630 ($C{=}N^+$); δ_H ($CDCl_3$-DMSO-d_6) 9.9 (s, IH), 9.I (br s, IH), 8.7-7.0 (m, 6H), 4.7 (t, IH, J=2Hz), 2.4 (d, 2H, J=2Hz).

Attempted Oxidative Decarboxylation of 3,4-Dihydro-β-carboline-3-carboxylic Acid (I08).

(a) Potassium Dichromate Oxidation.

A solution of potassium dichromate (0.79g, 0.003 mole) in water (I0ml) and glacial acetic acid (I0ml), was added dropwise to a solution of the perchlorate salt (I08) (I.0g, 0.003 mole) in water (50ml) at room temperature. The solution rapidly went dark brown and after 60 minutes the solution was extracted with chloroform, the chloroform solution dried over magnesium sulphate and evaporated under reduced pressure to give a black tar. The reaction was abandoned.

Repetition of the above reaction at 0°C gave the same black tar.

(b) Sodium Hypochlorite Oxidation.

A solution of the perchlorate salt (I08) (I.0g, 0.003 mole) in water (I00ml) was treated with chloroform (I50ml) and then with aqueous sodium hypochlorite solution (I3ml, I0% available chlorine). The mixture

was stirred for two hours, the chloroform layer separated, dried over magnesium sulphate and evaporated under reduced pressure to yield a black tar. The reaction was abandoned.

Repetition at $0^{o}C$ yielded the same black tar.

Attemted Hydrolytic Decarboxylation of 3,4-Dihydro-β-carboline-3-carboxylic acid (I08).

A solution of sodium carbonate (5.3g, 0.05 mole) in water (25ml) was added dropwise to a vigorously stirred mixture of the perchlorate salt (I08) (5.0g, 0.0I5 mole), water (I50ml), chloroform (I50ml) and benzyltriethyl-ammonium hydroxide solution (0.5g). After 24 hours at room temperature the chloroform layer was separated and dried over magnesium sulphate. The TLC of the chloroform layer showed no spots and evaporation of the solution under reduced pressure gave no residue. The procedure was abandoned.

2-Methyl-β-carbolinium Iodide(I42).

β-Carboline (7) (5.0g, 0.03 mole) and iodomethane (6.0g, 0.042 mole) were refluxed in acetone (75ml) for one hour. On cooling, the product (I42) crystallised out as yellow needles (7.6g 85%), m.p. 234-6°C (Lit.[I73] 235°C); λ_{max} (ε_{max}) 222nm (22 850), 256 (28 990), 3I0 (I7 440), 390 (I0 070); ν_{max} I640 cm^{-I} ($C{=}N^{+}$); δ_{H} (DMSO-d_6) 9.85 (s, IH), 9.32 (s, IH), 8.6-8.2 (m, 3H), 7.88-7.7 (m, 2H),

7.6-7.4 (m, IH), 4.52 (s, 3H).

9-Benzenesulphonyl-2-methyl-β-carbolinium Chloride (I43).

2M Sodium hydroxide solution (I5ml) was added dropwise to a cooled solution of 2-methyl-β-carbolinium iodide (I42) (I0.0g, 0.033 mole) in water (I00ml). The solution was extracted with chloroform, the organic extract dried over magnesium sulphate and evaporated under reduced pressure. The residue was dissolved in toluene, treated with benzenesulphonyl chloride (5.7g, 0.035 mole) and the resulting suspension stood overnight at room temperature. Evaporation under reduced pressure afforded a red oil which gave a yellow solid on trituration with ether. Recrystallisation from ethanol-ether gave (I43) (6.3g 53%) as pale yellow plates, m.p. I62-4°C; λ_{max} (ε_{max}) 209 nm (26 I50), 2I8 (25 950), 260 (I0 650), 30I (I6 050), 348 (4 350); ν_{max} I640 cm^{-I} ($C{=}N^{+}$), I375, II80 (SO_2N); δ_H (DMSO-d_6) 9.2 (d, IH, J=6Hz), 8.84 (d, IH, J=6Hz), 8.5-8.I8 (m, 5H), 8.02-7.84 (m, IH), 7.7-7.52 (m, 4H), 4.84 (s, 3H); Found C 60.45%, H 4.59%, N 7.38%, $C_{I8}H_{I5}ClN_2O_2S$ requires C 60.24%, H 4.2I%, N 7.8%.

Attempted Synthesis of 9-Benzenesulphonyl-2-methyl-I,2-dihydro-β-carboline (I60) and Reaction with Various Aromatic Acid Chlorides.

(a) Lithium Aluminium Hydride in Ether.

A stirred suspension of finely powdered (I43) (0.75g, 0.002 mole) in dry ether (50ml) was treated, under nitrogen, with solid lithium aluminium hydride (0.38g, 0.0I mole). After two hours a further portion of lithium aluminium hydride (0.I9g, 0.005 mole) was added and the suspension stirred for a further 22 hours. The excess hydride was decomposed by the dropwise addition of saturated potassium sodium tatrate solution (I0ml) and the ether layer decanted off and dried over magnesium sulphate. The ultra-violet spectrum of this ether solution showed no absorbance.

The aqueous layer from the work up was extracted with dichloromethane (5 X 50ml), and the combined extracts dried over magnesium sulphate and evaporated under reduced pressure to yield a yellow solid (0.7g). The spectral characteristics of this product were identical to those of the starting material.

(b) Lithium Aluminium Hydride in Tetrahydrofuran.

Lithium aluminium hydride (0.38g, 0.0I mole) was added to a stirred suspension of finely powdered (I43) (0.75g, 0.002 mole) in dry tetrahydrofuran (50ml), and the mixture stirred under nitrogen for two hours. A further portion of lithium aluminium hydride (0.I9g, 0.05 mole) was added and the suspension stirred for another three hours. The excess hydride was decomposed

by the dropwise addition of saturated potassium sodium tartrate solution (IOml) and the pale yellow organic layer (which rapidly turned orange on exposure to air) was decanted off and dried over magnesium sulphate. The ultra-violet spectrum of this solution showed absorptions at 205, 238 and 288 nm.

Reaction with Benzoyl Chloride.

The tetrahydrofuran solution was filtered under nitrogen and the filtrate treated with triethylamine (0.28ml, 0.002 mole) and benzoyl chloride (0.28g, 0.002 mole). After stirring overnight, the solution was evaporated under reduced pressure, the residue triturated with water and filtered to yield an off-white solid (0.I5g) which proved to be benzoic acid.

Reaction with 4-Nitrobenzoyl Chloride.

The tetrahydrofuran solution was filtered under nitrogen and the filtrate treated with triethylamine (0.28ml, 0.002 mole) followed by 4-nitrobenzoyl chloride (0.37g, 0.002 mole). After stirring overnight, the solution was evaporated under reduced pressure and the residue triturated with water and filtered to give an orange solid (0.086g), m.p. 94-I00°C; m/z (%) 473 (3), 472 (I0), 443 (27), 332 (3I), 302 (47), 2I0 (30), I57 (20), I40 (23), 99 (I7), 46 (I00).

(c) Sodium Borohydride in Dimethylformamide.

9-Benzenesulphonyl-2-methyl-β-carbolinium chloride

(I43) (0.5g, 0.00I3 mole) was added to a suspension of sodium borohydride (0.Ig, 0.0026 mole) in dry dimethylformamide (I5ml), containing 4A molecular sieve (0.5g), and the mixture stirred for three hours at room temperature under nitrogen. Excess sodium borohydride was decomposed by the addition of water (Iml), the solution diluted with ether (I00ml) and dried over magnesium sulphate. The solution was filtered under nitrogen and the filtrate treated with triethylamine (0.I8ml, 0.00I3 mole) and 4-nitrobenzoyl chloride (0.24g, 0.00I3 mole) and stirred overnight. The mixture was poured into water (200ml), the ether layer separated and the aqueous layer extracted with ether (3 X 75ml). The combined ether extracts were washed with water and dried over magnesium sulphate. Evaporation under reduced pressure afforded a red oil. The TLC showed two spots (Rf 0.55 and 0.65, silica/ ethyl acetate-petrol 9:I). Column chromatography on silica using the same solvent system gave an orange solid which gave orange plates (0.034g) from acetone-petrol; ν_{max} I7I0 cm^{-I}; δ_H (DMSO-d_6) correct integration for the proposed stucture.

(d) Sodium Borohydride in Methanol.

A solution of 9-benzenesulphonyl-2-methyl-β-carbolinium chloride (I43) (0.5g, 0.00I3 mole) in methanol (25ml) was treated with sodium borohydride (0.Ig, 0.0026 mole) and the solution stirred at room temperature for

three hours. The ultra-violet spectrum of the solution showed absorptions characteristic of a substituted indole indicating complete reduction. The solution was acidified with 2M hydrochloric acid, to decompose any excess sodium borohydride, basified with ammonium hydroxide and extracted with chloroform (3 X 100ml). The combined chloroform extracts were dried over magnesium sulphate, evaporated under reduced pressure and the resulting pale yellow solid recrystallised from methanol to yield 2-methyl-1,2,3,4-tetrahydro-β-carboline (53) (0.15g, 62%) as off-white needles, m.p. 215-6°C (Lit.[116] 217-8°C); λ_{max} (ε_{max}) 236 nm (6 710), 283 (7 890), 290 (shd, 6 830); ν_{max} 3400 cm^{-1} (NH); δ_H (DMSO-d_6) 9.9 (s, 1H), 7.44-7.21 (m, 2H), 7.06-6.94 (m, 2H), 3.54 (s, 2H), 2.74 (s, 4H), 2.46 (s, 3H).

2,9-Dimethyl-β-carbolinium Iodide (163).

2M Sodium hydroxide solution (15ml) was added dropwise to a cooled solution of 2-methyl-β-carbolinium iodide (142) (10.0g, 0.033 mole) in water (100ml). The solution was extracted with chloroform, the combined organic extracts dried over magnesium sulphate and evaporated under reduced pressure. The residue was dissolved in toluene (40ml) and nitrobenzene (40ml), treated with iodomethane (7.0g, 0.05 mole) and refluxed for one hour. The solution was cooled in a refrigerator

overnight and the resulting solid filtered off and re-crystallised from methanol-ether to give (I63) (8.Ig 77%) as yellow needles, m.p. 275-6°C (Lit.[190] 279°C); λ_{max} (ε_{max}) 22I nm (22 220), 260 (29 340), 3II (I6 240), 385 (7 I20); ν_{max} I640 cm^{-I} (C=N$^+$); δ_H (DMSO-d_6-D_2O) 9.32 (s, IH), 8.64-8.32 (m, 3H), 7.92-7.72 (m, 2H), 7.6-7.44 (m, IH), 4.5I (s, 3H), 3.96 (s, 3H).

Attempted Synthesis of 4-Benzoyl-2,9-dimethyl-I,2-dihydro-β-carboline (I65, R = X = H).

A suspension of 2,9-dimethyl-β-carbolinium iodide (I63) (0.65g, 0.002 mole) in dry THF (50ml) was treated under nitrogen with lithium aluminium hydride (0.38g, 0.0I mole) and the mixture stirred at room temperature for two hours. A further portion of lithium aluminium hydride (0.I9g, 0.005 mole) was added and the suspension stirred for a further three hours. The excess hydride was decomposed by the dropwise addition of saturated potassium sodium tartrate solution (IOml), and the pale yellow THF layer was decanted off and dried over magnesium sulphate. The solution was filtered under nitrogen and the filtrate treated with triethylamine (0.28ml, 0.002 mole) and benzoyl chloride (0.28g, 0.002 mole). After stirring at room temperature overnight, the solution was evaporated under reduced pressure and the residue triturated with water. The resulting red oil

was extracted with dichloromethane (3 X 50ml) and the combined organic extracts dried over magnesium sulphate. Evaporation under reduced pressure gave a red oil which was subjected to column chromatography on silica using 2% methanol in ethyl acetate, to afford a red oil (0.12g, 20%); m/z (%) 303 (18), 302 (7), 210 (35), 105 (100), 77 (74).

Attempted Synthesis of 2,9-Dimethyl-4-(4-nitrobenzyl)-β-carbolinium Perchlorate (169).

An etherial solution of 2,9-dimethyl-1,2-dihydro-β-carboline (164) was treated with glacial acetic acid (10ml) and 4-nitrobenzaldehyde (0.33g, 0.0022 mole), and the dark red solution refluxed under nitrogen for two hours. After standing at room temperature for a further 48 hours, the solvent was evaporated under reduced pressure, the residue triturated with water and extracted with dichloromethane (3 X 50ml). Drying over magnesium sulphate and ecaporation under reduced pressure, yielded a red oil which was treated, with ice cooling, with 70% perchloric acid solution. The resulting red solid was filtered off and air dried (0.25g, 29%), m.p. 200-5°C; ν_{max} 1640 cm^{-1}; m/z (%) 332 (2), 211 (42), 44 (100).

Attempted Synthesis of 4-Benzoyl-1-butyl-2,9-dimethyl-1,2-dihydro-β-carboline (165, R = C_4H_9, X = H).

A suspension of 2,9-dimethyl-β-carbolinium iodide (I63) (0.65g, 0.002 mole) in dry ether (50ml) was treated, under nitrogen, at -75°C, with n-butyllithium (I.6M in hexane, I.25ml, 0.002 mole) and the solution allowed to warm to room temperature over 45 minutes. The resulting pale yellow solution was treated with triethylamine (0.28ml, 0.002 mole) and benzoyl chloride (0.28g, 0.002 mole), After stirring at room temperature overnight, the solution was evaporated under reduced pressure and the residue triturated with water. Extraction with dichloromethane (3 X 50ml), drying of the organic extracts over magnesium sulphateand evaporation under reduced pressure afforded a red oil. Column chromatography on silica, using 2% methanol in ethyl acetate, gave the product (0.6g, 84%) as a yellow solid, m.p. I28-200°C. Several recrystallisations from ethyl acetate failed to improve the melting point. λ_{max} 267, 3I4, 400 nm; ν_{max} I660, I640 cm^{-I}; m/z (%) 358 (4), 357 (I2), 343 (30), 342 (II), 329 (I8), 328 (68), 3I5 (25), 3I4 (49), 30I (67), 300 (I00), 287 (4), 286 (9), I05 (63), 7I (49).

I-Benzenesulphonylindole (I85).

(a) Dimethylsulphoxide as Solvent.

Dimethylsulphoxide (I20ml) was added dropwise to a stirred suspension of 50% sodium hydride (4.8g, 0.I mole) in ether (50ml), and the solution warmed to 60-70°C for

one hour. The resulting green solution was cooled to 0-5°C, indole (II.7g, 0.I mole) in ether (50ml) was added dropwise and the solution stirred at room temperature for 30 minutes. The reaction mixture was cooled in ice, benzenesulphonyl chloride (I9.4g, 0.II mole) in ether (50ml) added dropwise and the solution stirred at room temperature for a further 30 minutes. The mixture was poured into water (I000ml) and extracted with ether (3 X I00ml), the combined organic extracts dried over magnesium sulphate and evaporated under reduced pressure to yield an orange oil which solidified on trituration with ether. Recrystallisation from hexane-dichloromethane yielded (I85) (I6.4g, 64%) as white crystals:

(b) Tetrahydrofuran as Solvent.

A solution of indole (II.7g, 0.I mole) in tetrahydrofuran (50ml) was added dropwise to a stirred suspension of 50% sodium hydride (4.8g, 0.I mole) in tetrahydrofuran (50ml). After stirring, at reflux, for one hour, benzenesulphonyl chloride (I9.4g, 0.II mole) in tetrahydrofuran (50ml) was added dropwise and the resulting suspension refluxed for a further two hours. The cooled reaction mixture was poured into water (500ml) the organic layer separated and the aqueous layer extracted with ether (3 X I00ml). The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to afford and orange oil which solidified

on trituration with ether. Recrystallisation from hexane-dichloromethane yielded (I85) (22.Ig, 86%) as white needles, m.p. 76-8°C (Lit.[I77] 77-9°C); λ_{max} (ε_{max}) 252 nm (5 330), 275 (shd), 285 (shd), 293 (shd, 2 900); ν_{max} I370, II70 cm^{-I} (SO_2N); δ_H ($CDCl_3$) 8.02-7.92 (m, IH), 7.83 (dd, 2H, J = 2Hz, 8Hz), 7.52 (d, IH, J = 4Hz), 7.46-7.24 (m, 3H), 7.24-7.I3 (m, d, 3H, J = 2Hz), 6.62 (d, IH, J = 4Hz); m/z (%) 257 (83), I4I (25), II6 (I00), 77 (47).

I-Benzenesulphonylindole-2-carboxaldehyde (I86).

(a) Butyllithium.

A solution of I-benzenesulphonylindole (I85) (3.Ig, 0.0I2 mole) in dry tetrahydrofuran (50ml) was treated, at -25°C under nitrogen, with a I.6M solution of n-butyllithium in hexane (7.5ml, 0.0I2 mole) dropwise from a syringe. The solution was allowed to warm to room temperature over one hour, cooled to 0°C and treated dropwise with a solution of N-methyl-formanilide (I.62g, 0.0I2 mole) in dry tetrahydrofuran (25ml), and the solution refluxed under nitrogen for three hours. The cooled solution was hydrolised with saturated ammonium chloride solution, the organic layer separated and the aqueous layer extracted with ethyl acetate (4 X I00ml). The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to afford a pale red oil which yielded a small ammount of a white

solid on trituration with ether-hexane. The solid was shown to be the starting material. The remaining oil was not identified.

(b) Lithium Diisopropylamide.

A solution of diisopropylamine (I2.6ml, 0.09 mole) in tetrahydrofuran (I00ml) was cooled to -72°C and treated dropwise, under nitrogen, with a I.6M solution of n-butyllithium in hexane (53ml, 0.084 mole) over I0 minutes, maintaining the temperature below -60°C. After 30 minutes I-benzenesulphonylindole (I85) (20.0g, 0.08 mole) in tetrahydrofuran (I50ml) was added dropwise at -60° to -70°C, the resulting solution stirred at -72°C for 90 minutes, warmed to 5°C over one hour then recooled to -72°C. Dimethylformamide (4.2ml, 0.08 mole) was added and the reaction mixture allowed to warm to room temperature overnight. The dark red solution was treated with saturated ammonium chloride solution, the organic layer separated and the aqueous layer extracted with ethyl acetate (4 X I00ml). The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to yield a red oil. The TLC (silica/ether) showed two spots at Rf 0.46 and Rf 0.6 (starter). Column chromatography on silica using I:3 hexane-ether gave (I86) (I0.3g, 45%) as an orange oil; ν_{max} I735 cm^{-I} (CO); δ_H ($CDCl_3$) 8.0-7.77 (m, 3H), 7.52-7.2 (m, 7H), 7.6 (d, IH, J = 4Hz); found C 64.4%, H 4.0%, N 5.I%,

$C_{15}H_{11}NO_3S$ requires C 63.1%, H 3.8%, N 4.9%; GLC (2% OV225, 200°C) 95% pure.

2,4-Dinitrophenylhydrazone (196).

Orange solid from glacial acetic acid, m.p. 218-20°C; found C 53.05%, H 2.82%, N 14.45%, $C_{21}H_{15}N_5O_6S$ requires C 54.19%, H 3.25%, N 15.05%; m/z (%) 465 (0.5), 324 (8), 278 (4), 129 (26), 77 (100).

N-(2,2-Diethoxyethyl)-(1-benzenesulphonyl)-2-indolylmethylamine (187, R = C_2H_5).

A solution of 1-benzenesulphonylindole-2-carboxaldehyde (8.1g, 0.028 mole) and aminoacetaldehyde diethylacetal (4.1ml, 0.028 mole) in toluene (200ml), containing a trace of para-toluenesulphonic acid, was azeotroped under a Dean-Stark head for 12 hours. The cooled solution was washed with 5% sodium carbonate solution (50ml) and evaporated under reduced pressure. The residue was dissolved in ethanol (100ml) and treated with sodium borohydride (0.8g, 0.02 mole). After stirring for one hour at room temperature, the solution was poured into water (500ml), carefully acidified with 2M hydrochloric acid and extracted with ether. Drying over magnesium sulphate and evaporation under reduced pressure gave a dark brown oil (7.1g) which proved to be the starting aldehyde and some 1-benzenesulphonylindole. The aqueous solution was basified with 2M ammonium hydroxide and

extracted with ethyl acetate. Drying over magnesium sulphate and evaporation under reduced pressure gave a brown oil (5.Ig). Column chromatography on silica, using I:3 hexane-ether, gave a red oil (2.3g, 30% based on recovered aldehyde); ν_{max} 3360 cm^{-I} (NH); δ_H ($CDCl_3$) 8.I4-8.04 (m, IH), 7.7-7.7 (m, 2H), 7.4-7.I5 (m, 7H), 6.55 (s, IH), 4.55 (t, IH, J = 4Hz), 4.I2 (s, 2H), 3.58 (q, 4H, J = 6Hz), 2.72 (d, 2H, J = 4Hz), I.2 (t, 6H, J = 6Hz); m/z (%) 402 (I), 356 (40), 327 (24), 270 (63), 206 (38), I67 (23), I30 (66), I03 (I00), 77 (72); found C 62.65%, H 6.77%, N 6.85%, $C_{2I}H_{26}N_2O_4S$ requires C 62.66%, H 6.5I%, N.6.96%.

N-(2,2-Diethoxyethyl)-N-methyl-(I-benzenesulphonyl)-2-indolylmethylamine (I88, R = C_2H_5).

A solution of (I87) (II.6g, 0.028 mole) in dioxan (50ml) was added dropwise to a stirred suspension of 80% sodium hydride (0.9g, 0.03 mole) in dioxan (50ml), and the mixture refluxed for one hour. Iodomethane (I.8ml, 0.028 mole) in dioxan (25ml) was added dropwise and the solution refluxed for a further three hours. The cooled reaction mixture was then treated with water and extracted with dichloromethane (3 X 50ml). The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to afford a brown gum. Column chromatography on silica, using I:3 hexane-ether, afforded

(I88) (9.8g, 84%) as a red oil; ν_{max} I360 cm^{-I} (SO_2N); δ_H ($CDCl_3$) 8.I-7.8 (m, 2H), 7.33-7.I (m, 6H), 6.58 (s, IH), 4.58 (t, IH, J = 4Hz), 3.92 (s, 2H), 3.5 (q, 4H, J = 7Hz), 2.62 (d, 2H, J = 4Hz), 2.24 (s, 3H), I.I5 (t, 6H, J = 7Hz); found C 63.45%, H 7.02%, N 6.6I%, $C_{22}H_{28}N_2O_4S$ requires C 63.44%, H 6.78%, N 6.73%.

Attempted Cyclisations of N-(2,2-Diethoxyethyl)-N-methyl-(I-benzenesulphonyl)-2-indolylmethylamine (I88, R = C_2H_5).

Method A.

A solution of the acetal (I88) (0.75g, 0.00I8 mole) in ethanol (IOml) and water (5ml), was treated with concentrated hydrochloric acid (5ml) and stirred at room temperature overnight. Benzaldehyde (0.2ml, 0.00I8 mole) was then added and the solution heated on a steam bath for three hours. The cooled solution was diluted with water (50ml) and extracted with dichloromethane (3 X 50ml). The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to afford a brown oil. Treatment of this oil, suspended in a little methanol, with 70% perchloric acid gave a brown solid (0.55g, 62%). Attempted recrystallisation led to loss of product or no improvement in spectra. The procedure was abandoned.

Method B.

A solution of the acetal (I88) (0.75g, 0.00I8 mole) and 3-nitrobenzaldehyde (0.3g, 0.00I8 mole) in dioxan

4-(3-Nitrobenzyl)-2-methyl-g-carbolinlum Tetrafluoroborate Monohydrate (191, Ar = 3-N0„C^H^

A solution of the acetal (190) (0.6g, 0.0022 mole) and 3-nitrobenzaldehyde (0.33g, 0.0022 mole) in ethanol (50ml) was treated with 4-0% tetrafluoroboric acid solution (2ml) and refluxed for I8 hours. The cooled solution was diluted with water (150ml) and extracted with dichloro-methane (3 X lOOml), Dryingof the organic extracts over magnesium sulphate and evaporation under reduced pressure gave a red gum. Recrystallisation from ethanol-water gave the monohydrate of (191) (O.I9g, 21%) as a yellow solid, m.p. 262-4°C;3 (disc) 3320 cm"^ (OH), I64O (C=N+);6y (DMSO-dg) 9.32 (s, IH), 8.46 (s, IH), 8.3-8.05 (m, 3H), 7.8-7.6 (m, 3%), 7.5-7.3 (m. 2H), 4.95 (s, 2H), 4.45 (s, 3H), 3.26 (br s, 2H); found C 53.9%, H 3.55%, N 9.5%, CjgHj-gBF^N^Og.IH^O requires C 53.9%, H 4.2%, N 9.9%.

4»(2-Chlorobenzyl)-2-methyl-P-carbolinium Tetrafluoro-borate (191, Ar = 2-ClC^H^)_^

Method as above using 2-chlorobenzaldehyde (0.3g, 0.0022 mole) gave the product (O.Ig, 11.5%) as a brown solid, m.p. 2I3-5°C;D^^^ (disc) I64O cm ^ (C=N^);Sg (DMSO-d.) 9.32 (s, IH), 8.3-7.0 (m, lOH), 4-79 (s, 2H), 4.45 (s, 3H); found C 57.2%, H 4.0%,, N 7.0%, C^^H^^BCIF^ requires C 57.7%, H 4.0%, N 7.0%.

2-Nitrophenypyruvic Acid (208).

Dry methanol (I6.0g, 0.5 mole) was added dropwise to a stirred suspension of sodium metal (II.5g, 0.5 mole) in dry ether (200ml), under nitrogen, and stirred until all the sodium had reacted. Dimethyl oxalate (59.0g, 0.5 mole) in dry methanol (I00ml) was added dropwise with cooling and followed by a solution of 2-nitrotoluene (68.5g, 0.5 mole) in ether (25ml). The deep red solution was stirred at room temperature for 24 hours, treated with 5M sodium hydroxide solution (I20ml, 0.6 mole), left for one hour and then acidified with 2M hydrochloric acid. The solution was extracted with ether (5 X I00ml), and the organic layer re-extracted with 2M sodium hydroxide solution (500ml). The aqueous solution was freed of ether by evaporation under reduced pressure, cooled in ice and acidified with concentrated hydrochloric acid to give (208) (54.6g, 52.3%) as yellow crystals, m.p. II3-4°C (Lit.[2I0,2II] II5°C); ν_{max} I760, I7I0 cm^{-I} (CO), I5I0 (NO_2); δ_H (DMSO-d_6) I0.99 (s, IH), 8.II (dd, IH, J = IHz, 8HZ), 7.67-7.37 (m, 3H), 4.77 (s, 2H).

Ethyl Pyruvate Phenylhydrazone (2I0).

Ethyl pyruvate (II.6g, 0.I mole) was added to a solution of phenylhydrazine hydrochloride (I4.4g, 0.I mole) in ethanol (200ml). Dry hydrogen chloride gas was passed through the solution as it was heated to reflux over one

hour. The solution was cooled and evaporated under reduced pressure to yield a brown solid which was recrystallised from ethanol-water to give (210) (15.2g, 74%) as a pale yellow solid, m.p. 104°C (Lit.,[210] 105°C); λ_{max} (ε_{max}) 241 nm (6 600), 295 (11 260), 330 (18 400); ν_{max} 3320, 3290 cm^{-1} (NH), 1710 (CO), 1690 (C N); δ_H (DMSO-d_6) 9.06 (s, 1H), 7.36-7.2 (m, 4H), 6.96-6.8 (m, 1H), 4.24 (q, 2H, J = 4Hz), 2.12 (s, 3H), 1.32 (t, 3H, J = 4Hz).

Ethyl Indole-2-carboxylate (209).

(a) From Ethyl Pyruvate Phenylhydrazone.

Ethyl pyruvate phenylhydrazone (210) (5.0g, 0.024 mole) was dissolved in glacial acetic acid (50ml) and concentrated sulphuric acid (1.0ml) and refluxed for one hour. The cooled solution was poured into water (500ml) and the mixture extracted with ether (5 X 100ml). The combined organic extracts were washed with water, saturated sodium carbonate solution and dried over magnesium sulphate. Evaporation under reduced pressure yielded an orange solid which was recrystallised from ethanol to give (209) (2.35g, 51.2%) as yellow plates, m.p. 110-112°C (Lit.,[210] 122°C).

(b) From Ethyl Pyruvate.

Ethyl pyruvate (58.0g, 0.5 mole) was added dropwise to an ice-cold, stirred solution of phenylhydrazine (54.0g, 0.5 mole) in glacial acetic acid (600ml) and

concentrated sulphuric acid (50ml). After stirring at room temperature for two hours, the solution was poured onto crushed ice (1000g) and extracted with ether (5 X 100ml). The combined organic extracts were washed with water, saturated sodium carbonate solution and dried over magnesiun sulphate. Evaporation under reduced pressure yielded an orange solid which was recrystallised from ethanol to yield (209) (70.8g, 75%) as yellow plates, m.p. 115-7°C (Lit.[210] 122°C); ν_{max} 3300 cm^{-1} NH), 1690 (CO); δ_H ($CDCl_3$) 9.4 (br s, 1H), 7.88 (s, 1H), 7.6-6.96 (m, 4H), 4,32 (q, 2H), 1.4 (t, 3H).

Indole-2-carboxylic Acid (205).

(a) From 2-Nitrophenylpyruvic Acid.

2-nitrophenylpyruvic acid (208) (40.0g, 0.19 mole) in 0.880 ammonia (250ml) and water (250ml) was treated with a solution of iron (II) sulphate (250g, 1.65 mole) in water (250ml), and the mixture boiled for one hour. The cooled solution was acidified with glacial acetic acid and the resulting solid filtered off. Recrystallisation from ethanol gave (205) (9.5g, 31%) as white needles, m.p. 204-5°C (Lit.[210] 204°C).

(b) From Ethyl Indole-2-carboxylate.

Ethyl indole-2-carboxylate (209) (20.0g, 0.11 mole) in 1M sodium carbonate solution (200ml) was bolied for two hours. The cooled solution was poured onto crushed

ice, acidified with 2M hydrochloric acid and the resulting solid filtered off. Recrystallisation from ethanol gave (205) (I7.2g, 78%) as white needles, m.p. 204-5°C (Lit.,[210] 204°C); λ_{max} (ε_{max}) 239 nm (7 520), 297 (I3 020); ν_{max} 3350 cm^{-1} (NH), I7I0 (CO); δ_H ($CDCl_3$) I0.3 (br s, IH), I0.I (br s, IH), 7.6-6.85 (m, 5H).

N-(2,2-Dimethoxyethyl)-N-methyl-indole-2-carboxamide (206).

Thionyl chloride (20.0g, 0.I67 mole) was added to a solution of indole-2-carboxylic acid (205) (I0.0g, 0.062 mole) in dry benzene (300ml), and the solution refluxed for four hours. The cooled solution was evaporated under reduced pressure and the residue dissolved in dry tetrahydrofuran (200ml) and treated with N-methylamino-acetaldehyde dimethylacetal (I4.8g, 0.I24 mole). After stirring at room temperature overnight, the suspension was treated with water (250ml) and extracted with ether. The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure. The residue was recrystallised from ethanol to give (206) (I3.7g, 84%) as pink crystals, m.p. 98-9°C; λ_{max} (ε_{max}) 2I8.5 nm (26 350), 237 (I5 250), 294 (I7 650); ν_{max} 3220 cm^{-1} (NH), I600 (CO); δ_H ($CDCl_3$) I0.08 (s, IH), 7.64 (d, IH, J = 8Hz), 7.44 (d, IH, J = 8Hz), 7.32-7.04 (m, 2H), 6.9 (d, IH, J = 3Hz), 4.68 (t, IH, J = 5Hz), 3.75 (d, 2H, J = 5Hz), 3.44 (s, 9H); found C 64.I%, H 6.92%,

N 10.7%, $C_{14}H_{18}N_2O_3$ requires C 64.1%, H 7.1%, N 10.7%.

N-(2,2-Dimethoxyethyl)-N-methyl-2-indolylmethylamine (190, R = CH_3).

The amide (206) (10.0g, 0.038 mole) in dry tetrahydrofuran (50ml) was added dropwise to a stirred solution of lithium aluminium hydride (0.8g, 0.021 mole) in dry tetrahydrofuran (50ml). The solution was stirred at room temperature, under nitrogen, till completion (TLC) - approximately three hours. The reaction mixture was treated consecutively with ether (100ml), water (2ml), 5M sodium hydroxide solution (2ml) and water (10ml). The resulting solid was filtered through kieselguhr, the precipitate washed with ether and the filtrate extracted with ether (3 X 50ml). The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to yield a red oil. Chromatography on silica, using ethyl acetate, gave (190) (6.45g, 68%) as a pale brown oil; ν_{max} 3350 cm^{-1} (NH); δ_H ($CDCl_3$) 8.78 (s, 1H), 7.58-7.48 (m, 1H), 7.36-7.18 (m, 1H), 7.12-7.01 (m, 2H), 6.32 (s, 1H), 4.48 (t, 1H, J = 4Hz), 3.72 (s, 2H), 3.32 (s, 6H), 2.58 (d, 2H, J = 4Hz), 2.32 (s, 3H).

1-Benzenesulphonylindole-2-carboxylic Acid (212).

1-Benzenesulphonylindole (185) (6.2g, 0.024 mole) in dry tetrahydrofuran (100ml) was cooled to -25°C, under

nitrogen, and treated dropwise with a I.6M solution of n-butyllithium in hexane (I5.0ml, 0.024 mole). After stirring for 30 minutes, the solution was added, carefully, to a slurry of solid carbon dioxide in dry ether (250ml) and left until all the carbon dioxide had evaporated. The resulting solution was acidified, by the careful addition of 2M hydrochloric acid, and extracted with dichloromethane (3 X I00ml). The combined dichloromethane extracts were dried over magnesium sulphate and evaporated under reduced pressure to afford a brown oil which solidified on trituration with hexane. Recrystallisation from dichloromethane-hexane gave (2I2) (4.I3g, 57%) as an off-white solid, m.p. I83-5°C (Lit.[I77] I88°C); ν_{max} 3200-2300 cm^{-I} (OH), I7I0 (CO); ^{H} (DMSO-d_6) I0.8-9.6 (br s, IH), 8.04 (dd, 2H, J = 8Hz, 2Hz), 7.6-7.I6 (m, 8H); m/z (%) 30I (3), 257 (23), I43 (I00), II6 (35), II5 (55), 89 (26), 77 (7I).

I-Benzenesulphonylindole-2-(N-(2,2-dimethoxyethyl)-N-methyl)-carboxamide (2I3).

I-Benzenesulphonylindole-2-carboxylic acid (9.0g, 0.03 mole), suspended in dry benzene (200ml), was treated with thionyl chloride (9.0g, 0.075 mole) and the mixture refluxed for three hours. The cooled solution was evaporated under reduced pressure and the residue treated with dry ether (I00ml) and N-methylaminoacetaldehyde

dimethylacetal (7.I4g, 0.06 mole) and the resulting suspension stirred at room temperature overnight. The reaction mixture was treated with water (500ml) and extracted with ether (3 X I00ml). The combined ether extracts were dried over magnesium sulphate and evaporated under reduced pressure to afford (2I3) (9.Ig, 70%) as an orange oil; ν_{max} I630 cm^{-I} (CO); δ_H ($CDCl_3$) 8.2-7.95 (m, 3H), 7.43-7.2 (m, 6H), 6.9-6.8 (m, IH), 4.93 (t, IH, J = 6Hz), 3.6 (d, 2H, J = 6Hz), 3.2 (s, 3H), I.2 (s, 6H).

N-(2,2-Dimethoxyethyl)-N-methyl-3-indolylmethylamine (2I4).

N-Methylaminoacetaldehyde dimethylacetal (I5.0g, 0.I25 mole) was added to an ice-cold solution of indole (I3.0g, 0.III mole) in glacial acetic acid (I00ml). The stirred solution was treated with a 35% aqueous solution of formaldehyde (3I.0g, 0.28 mole) and left for one hour at room temperature. After diluting with water (I00ml), the solution was extracted with ether (3 X 50ml) and the aqueous layer basified with 2M ammonium hydroxide solution. Extraction with chloroform (3 X I00ml), drying over magnesium sulphate and evaporation under reduced pressure yielded a red oil which solidified on cooling. Recrystallisation from benzene-hexane gave (2I4) (23.3g, 88%) as a white solid, m.p. 77-8°C (Lit.[2I3] 78-9°C); λ_{max} (ε_{max}) 23I nm (5 460), 250 (shd), 268 (shd), 275 (7 900), 283 (8 I90), 29I (6 820); ν_{max} 3I50 cm^{-I} (NH); δ_H 8.84 (s, IH),

7.74 (m, IH), 7.34-7.08 (m, 3H), 6.96 (d, IH, J = 2Hz), 4.56 (t, IH, J = 5Hz), 3.76 (s, 2H), 3.29 (s, 6H), 2.6I (d, 2H, J = 5Hz), 2.32 (s, 3H); found C 67.3%, H 7.9%, N IO.9%, $C_{I4}H_{20}N_2O_2$ requires C 67.7%, H 8.I2%, N II.28%.

4-Hydroxy-2-methyl-I,2,3,4-tetrahydro-β-carboline (2I7).

The acetal (2I4) (IO.0g, 0.05 mole) was treated with 6M hydrochloric acid (300ml) at 0°C, and was allowed to stand at this temperature for one hour. After stirring for a further 3.5 hours at room temperature, the reaction mixture was made alkaline with 2M ammonium hydroxide solution and extracted with chloroform (5 X IOOml). Drying of the combined organic extracts over magnesium sulphate and evaporation under reduced pressure afforded a solid. Recrystallisation from ethanol gave (2I7) (4.23g, 52%) as white needles, m.p. 202-3°C (Lit.[2I3] 205-7°C; λ_{max} (ε_{max}) 243 (5 660), 284 (6 800); ν_{max} 3400 cm^{-I} (OH), 3220 (NH); δ_H ($CDCl_3$) 9.88 (s, IH), 7.4-7.24 (m, 2H), 7.08-7.0 (m, 3H), 4.82 (t, IH, J = 5Hz), 3.8 (d, 2H, J = 5Hz), 3.5 (q, 2H, J = 4Hz), 2.48 (s, 3H).

Reduction of 4-Hydroxy-2-methyl-I,2,3,4-tetrahydro-β-carboline (2I7).

(a) Catalytic Reduction.

The hydroxy compound (2I7) (0.5g, 0.00247 mole) and 5% palladium on charcoal (0.Ig) in 6M hydrochloric

acid (100ml), were treated with hydrogen gas at atmospheric pressure and room temperature. After absorption of the theoretical amount of hydrogen, the solution was filtered through kieselguhr, the filtrate basified with concentrated ammonia solution and extracted with chloroform (3 X 100ml). Drying of the organic extracts over magnesium sulphate and evaporation under reduced pressure afforded a yellow solid. Recrystallisation from methanol gave (53) (0.179g, 39%), m.p. 215-6°C (Lit.[116] 217-8°C).

(b) Lithium Aluminium Hydride - Aluminium Chloride.

The hydroxy compound (217) (0.5g, 0.00247 mole) in dry di-n-butyl ether (25ml) was added to a solution of lithium aluminium hydride (0.235g, 0.0062 mole) and aluminium chloride (2.48g, 0.0186 mole) in di-n-butyl ether (100ml), and the mixture heated at 80°C for eight hours. The cooled mixture was poured onto crushed ice and the organic layer separated and dried over magnesium sulphate. Evaporation under reduced pressure afforded a yellow solid which was recrystallised from methanol to give (53) (0.322g, 63%), m.p. 215-6°C (Lit.[116] 217-8°C); ν_{max} 3400 cm^{-1} (NH); δ_H ($CDCl_3$) 10.24 (s, 1H), 7.4-7.0 (m, 4H), 3.6 (s, 2H), 2.76 (m, 4H), 2.52 (s, 3H).

Picrate:- crystals from ethanol, m.p. 195°C (decomp.) (Lit.[116] 197-8°C).

2-Methyl-I,2,3,4-tetrahydro-γ-carboline (2I8).

I-Methyl-4-piperidone (II.3g, 0.I mole) in glacial acetic acid (I00ml) was added dropwise to a cooled solution of phenylhydrazine hydrochloride (I4.5g, 0.I mole) in glacial acetic acid (I00ml) and concentrated sulphuric acid (5ml). The solution was warmed to 60°C, and after ohe hour at this temperature, was poured into water (I000ml) and basified with 2M ammonium hydroxide solution. Extraction with dichloromethane, drying over magnesium sulphate and evaporation under reduced pressure afforded a brown solid. Recrystallisation from methanol gave (2I8) (I5.0g, 83%) as pale yellow needles, m.p. I70-I°C (Lit.,[II6] I69-70°C); ν_{max} 3420 cm^{-I} (NH); δ_H ($CDCl_3$) 8.74 (s, IH), 7.42-7.0 (m, 4H), 3.64 (s, 2H), 2.76-2.64 (m, 2H), 2.52 (s, 5H).

Picrate:- pale yellow crystals from ethanol, m.p. I20°C (Lit.,[II6] I30-I°C).

2-Methyl-I,2,3,4-tetrahydro-β-carboline (53).

2-Methyl-β-carbolinium iodide (I42) (0.75g, 0.0024 mole) in methanol (25ml) and water (25ml) was treated with sodium borohydride (0.I9g, 0.005 mole) at 65°C. After 30 minutes the solution was cooled, the excess borohydride destroyed by the addition of 2M hydrochloric acid and the solution basified with 2M ammonium hydroxide solution. Extraction with chloroform, drying over

magnesium sulphate and evaporation under reduced pressure gave a yellow solid. Recrystallisation from methanol gave (53) (0.385g, 83%), m.p. 215-6°C (Lit.[II6] 217-8°C); ν_{max} 3400 cm^{-1} (NH); δ_H ($CDCl_3$) 9.9 (s, 1H), 7.44-7.0 (m, 4H), 3,54 (s, 2H), 2.78 (s, 4H), 2.46 (s, 3H).

Picrate:- crystals from ethanol, m.p. 206°C (Lit.[II6] 207-9°C).

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APPENDIX I

SPECTRA

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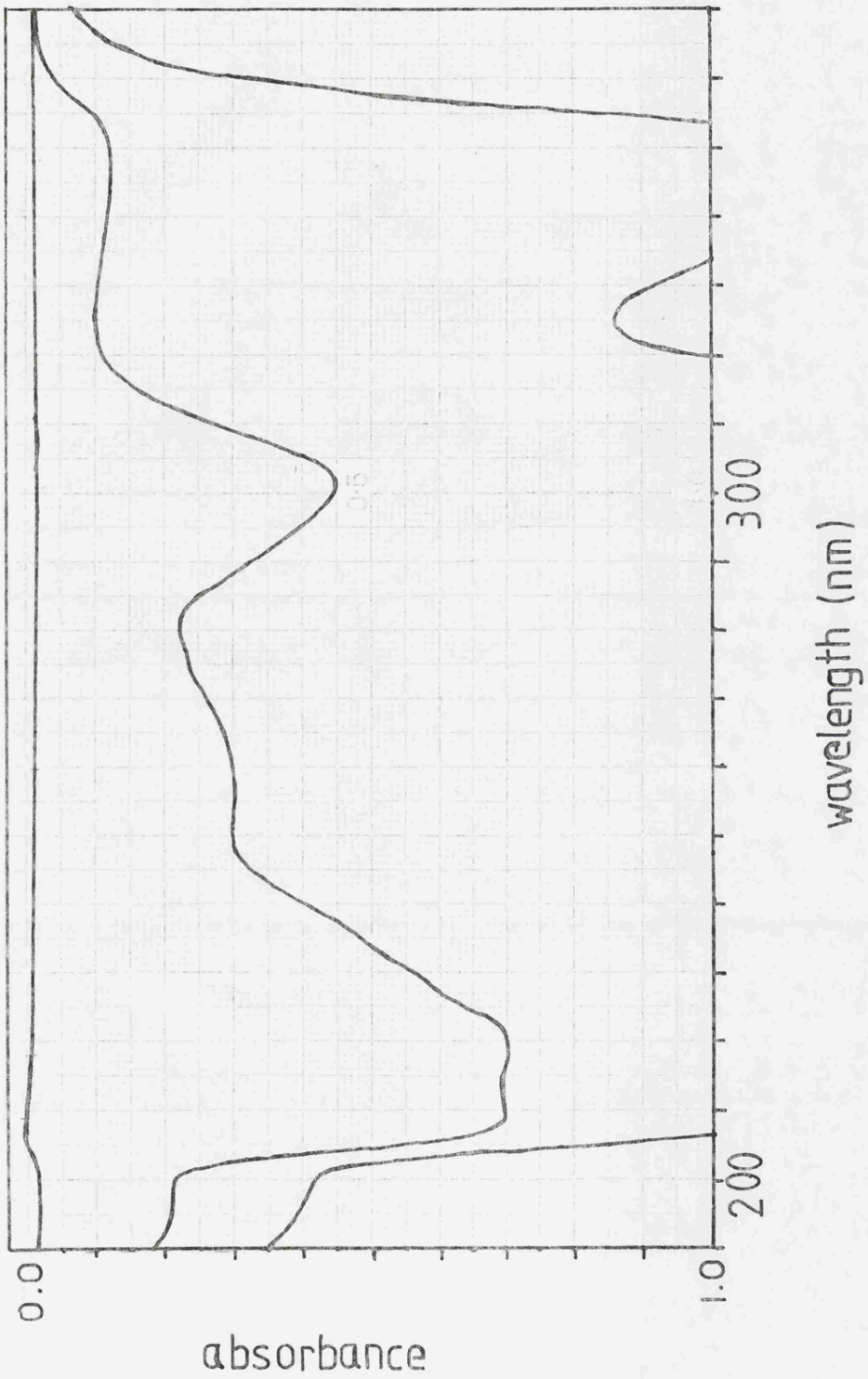
Spectrum I.



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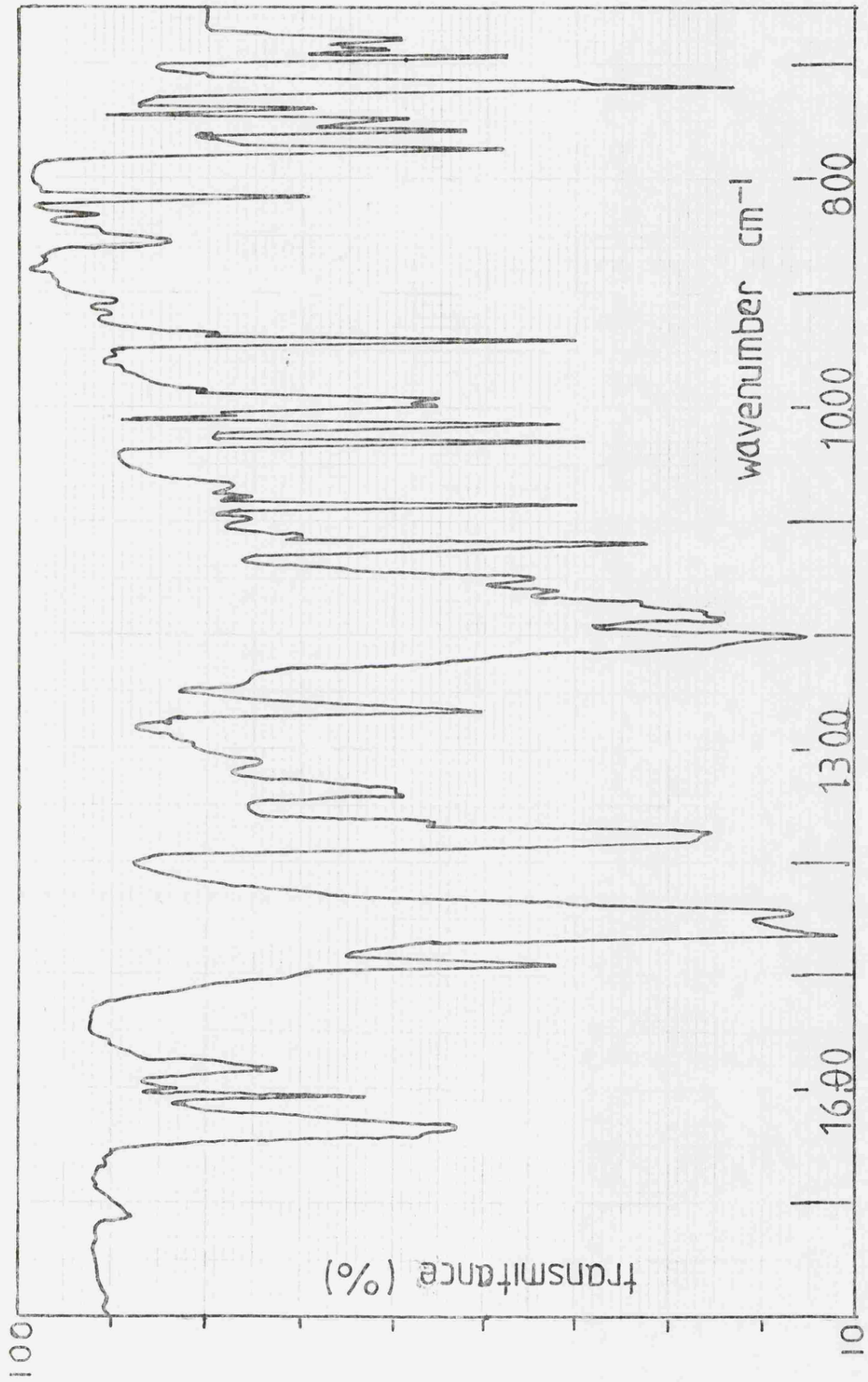

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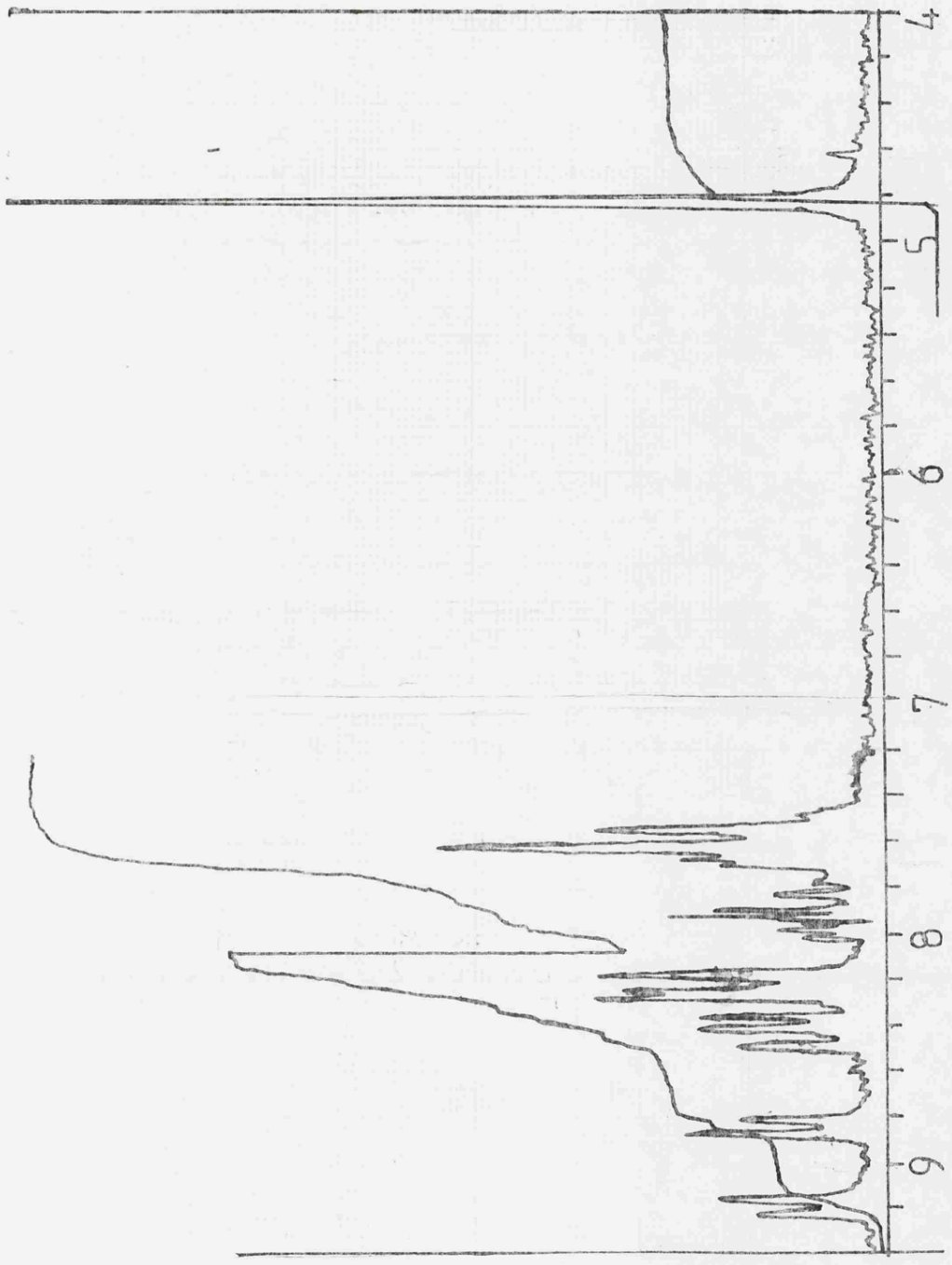

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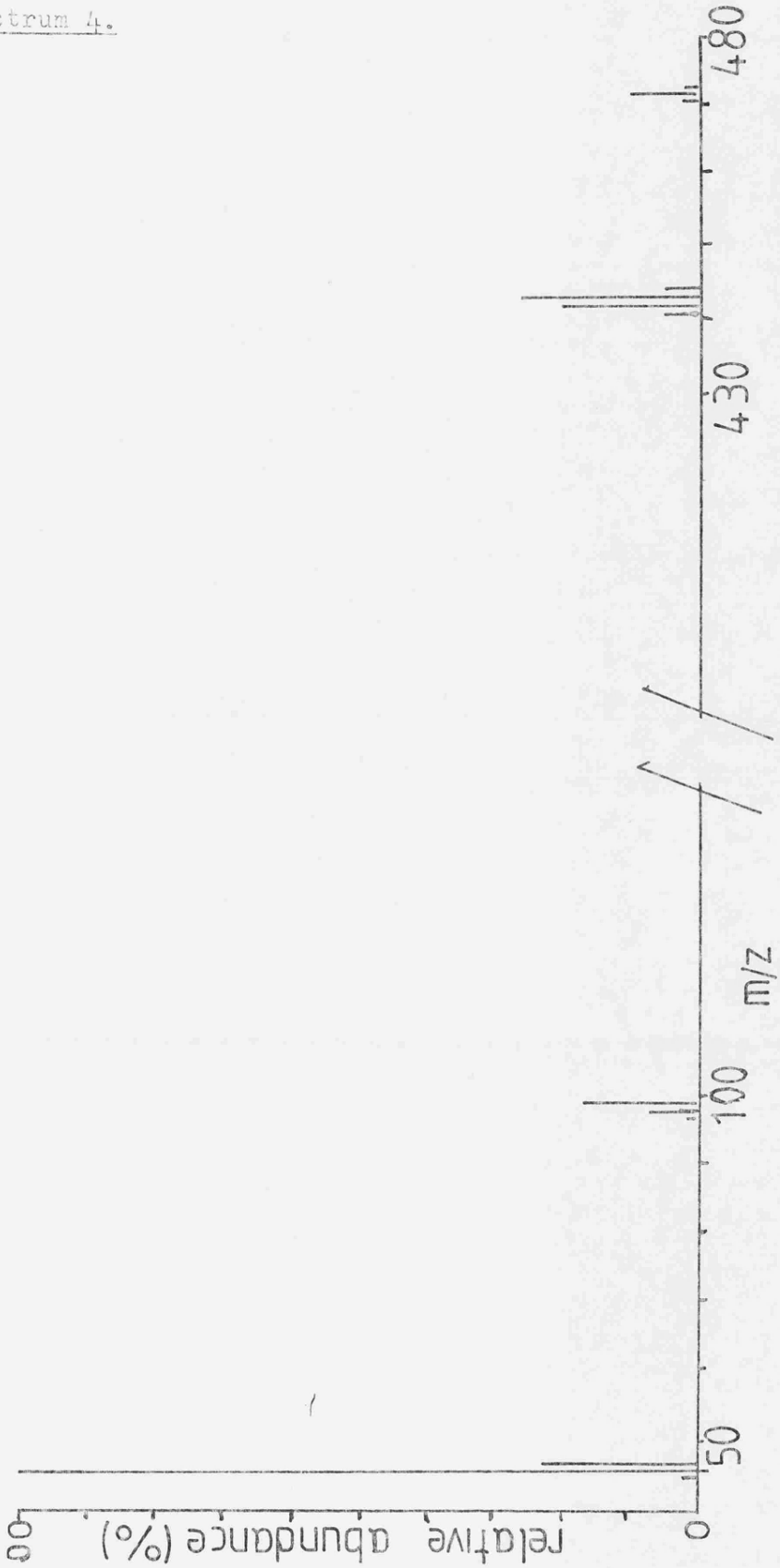

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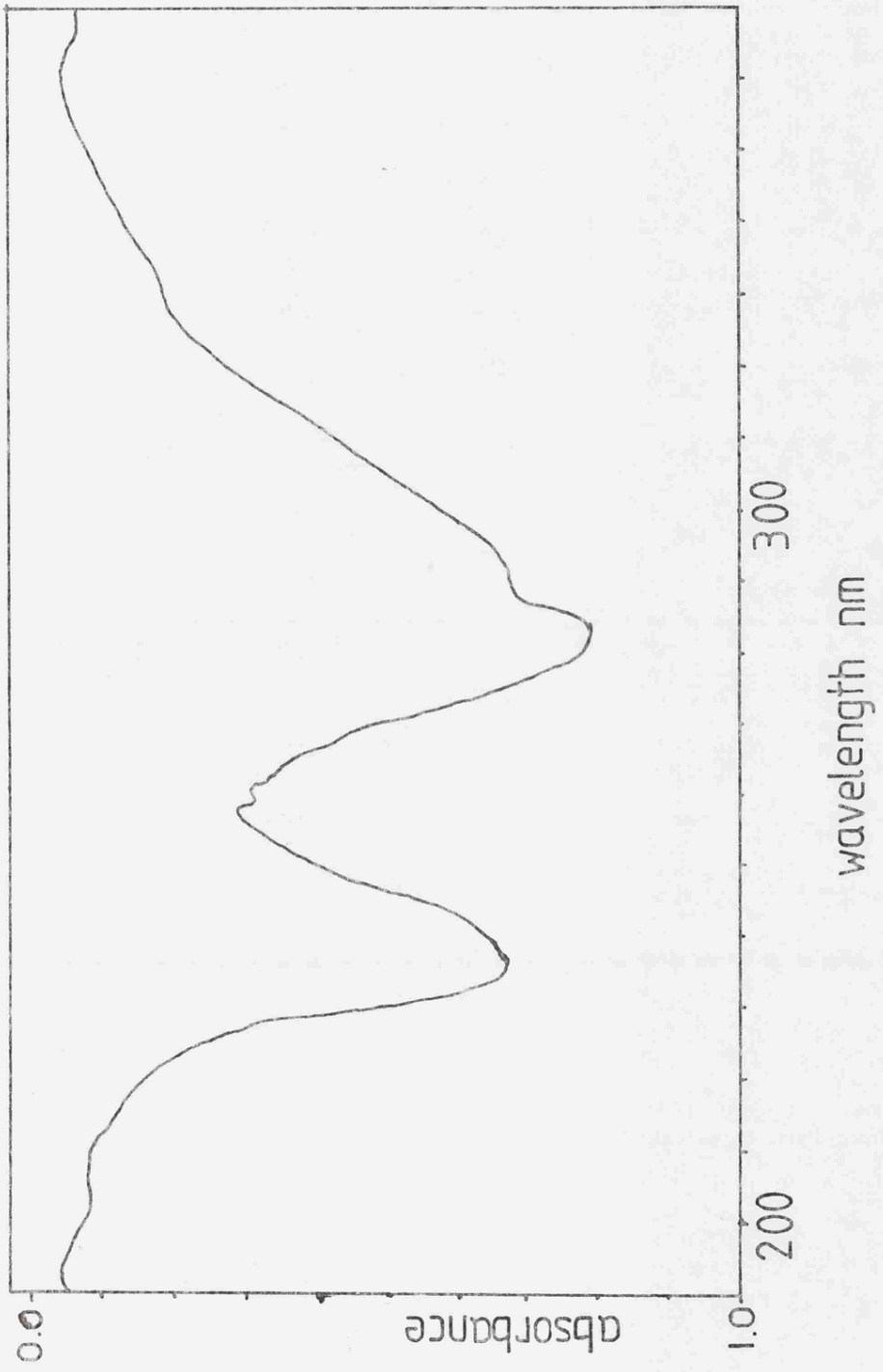

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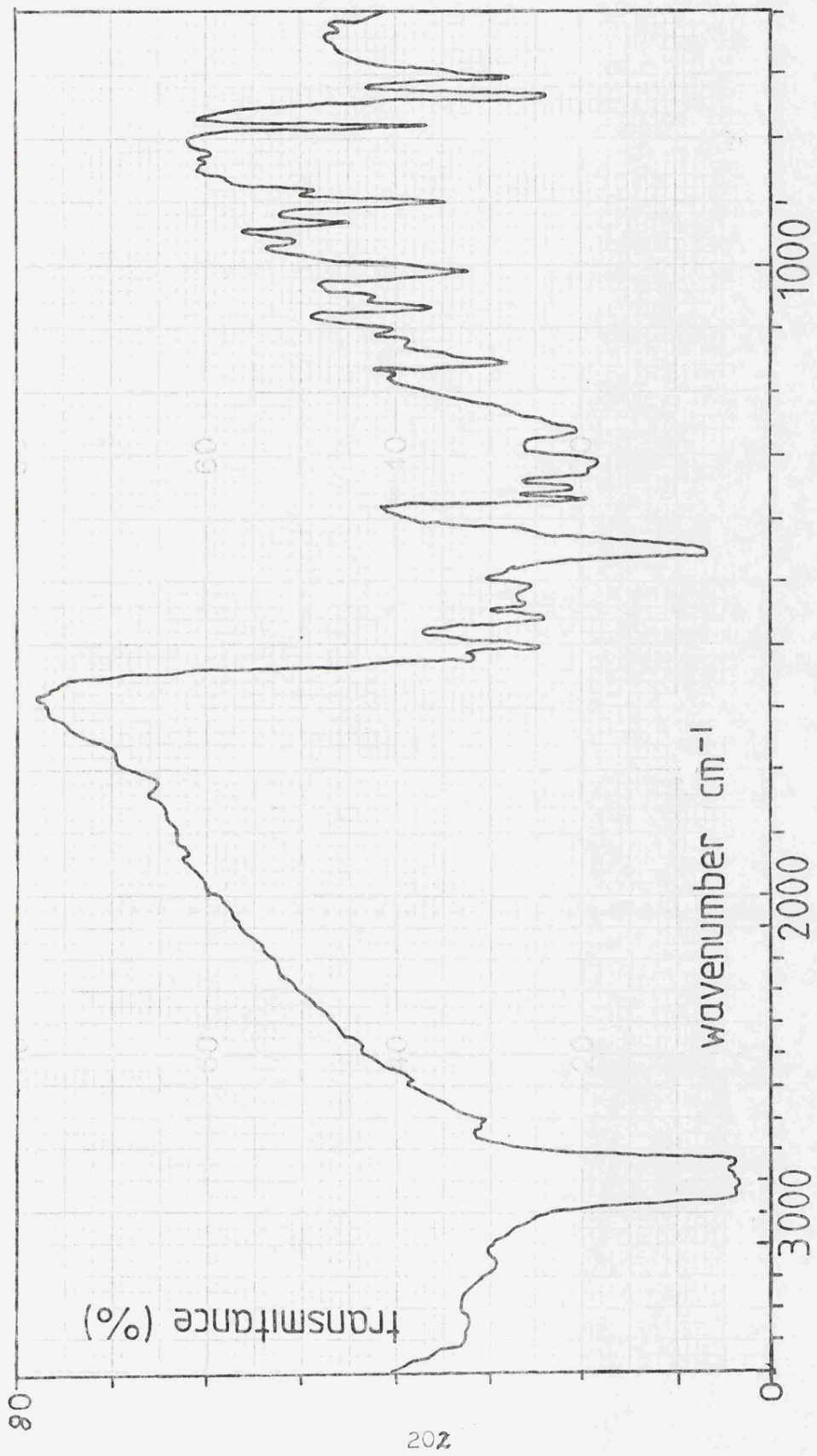

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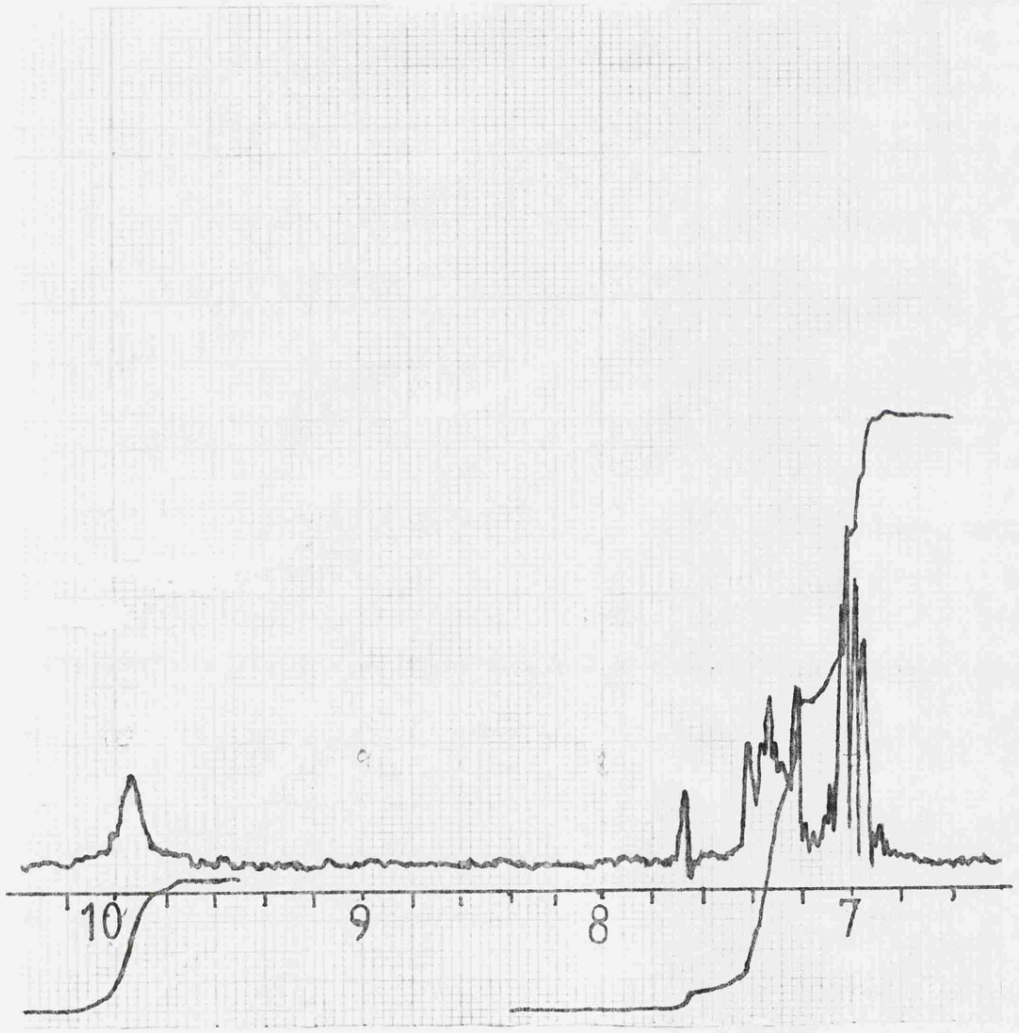

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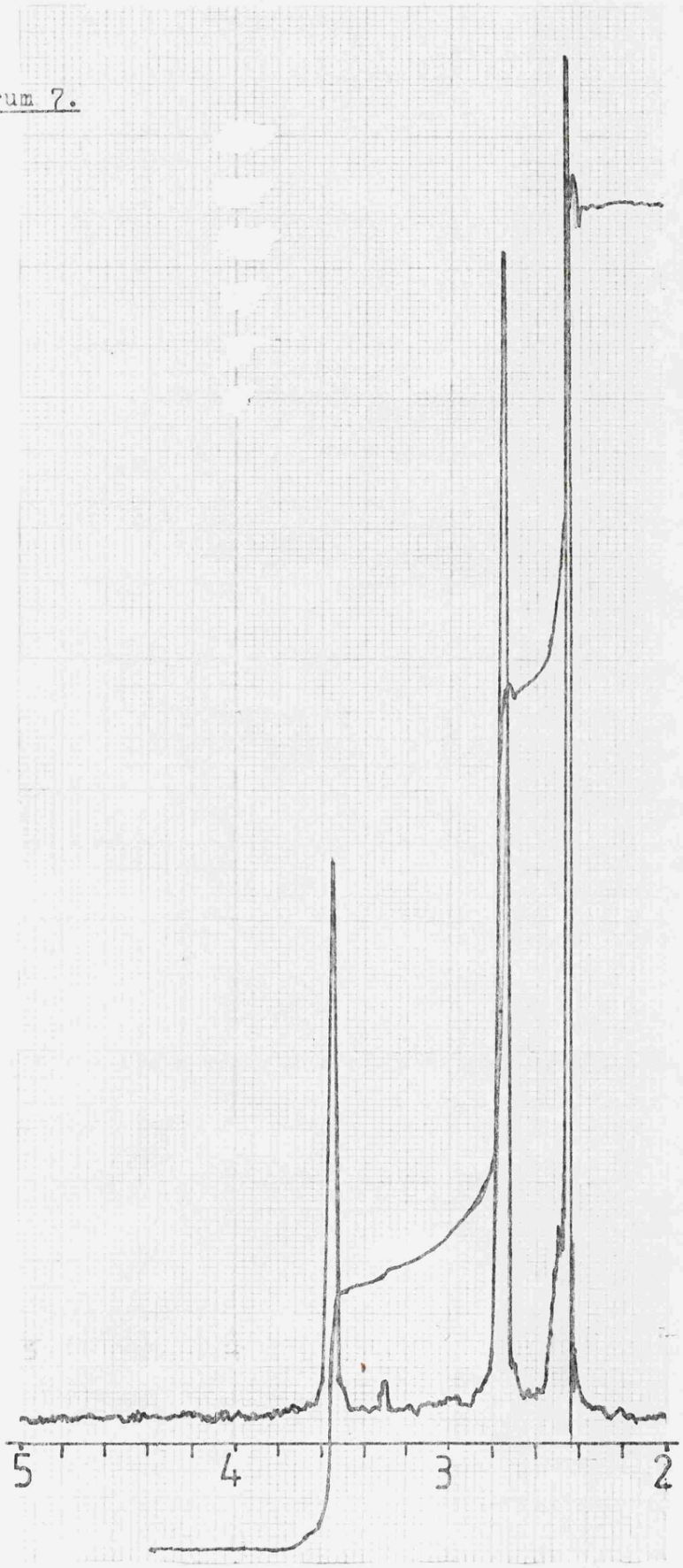

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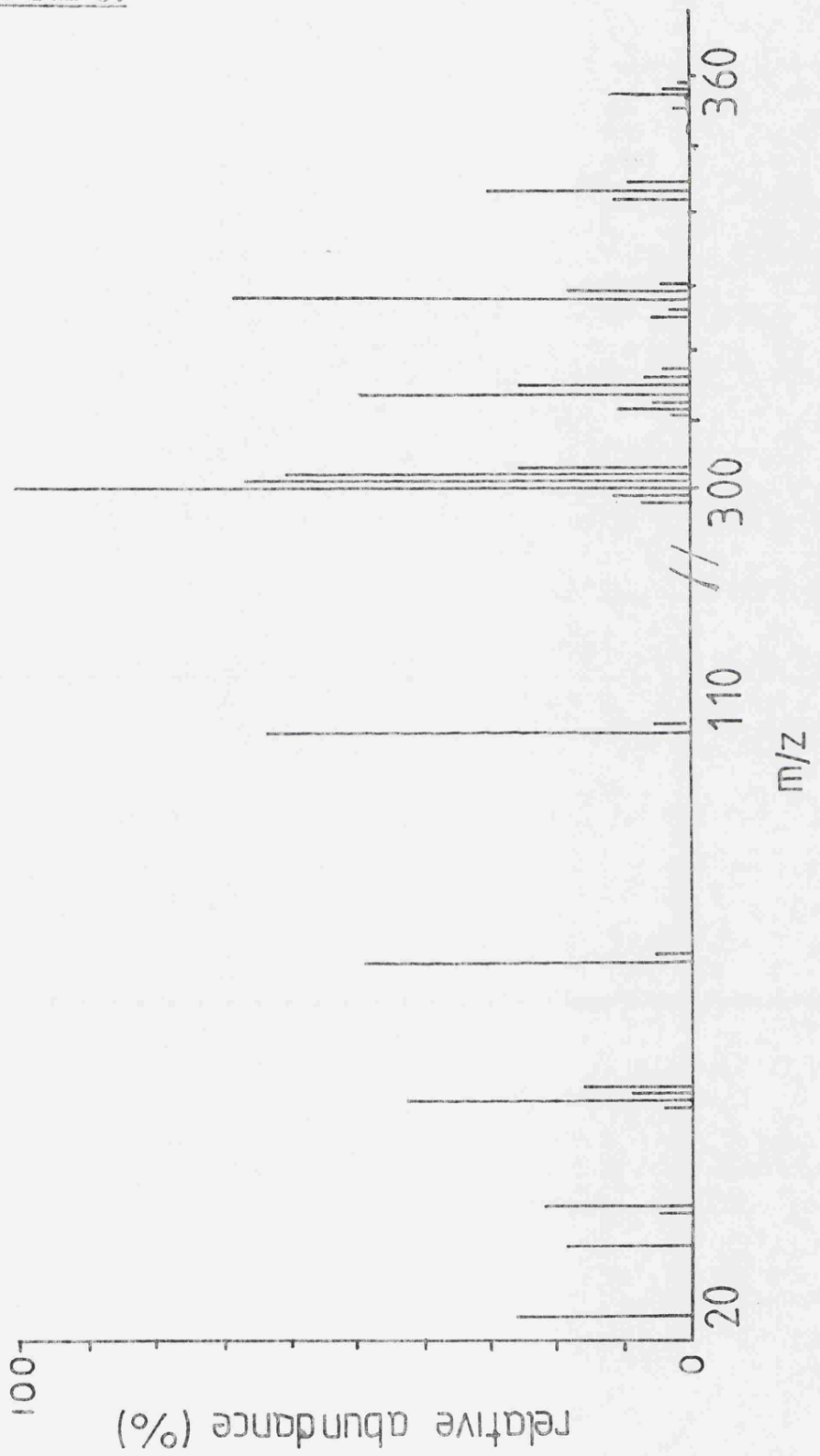

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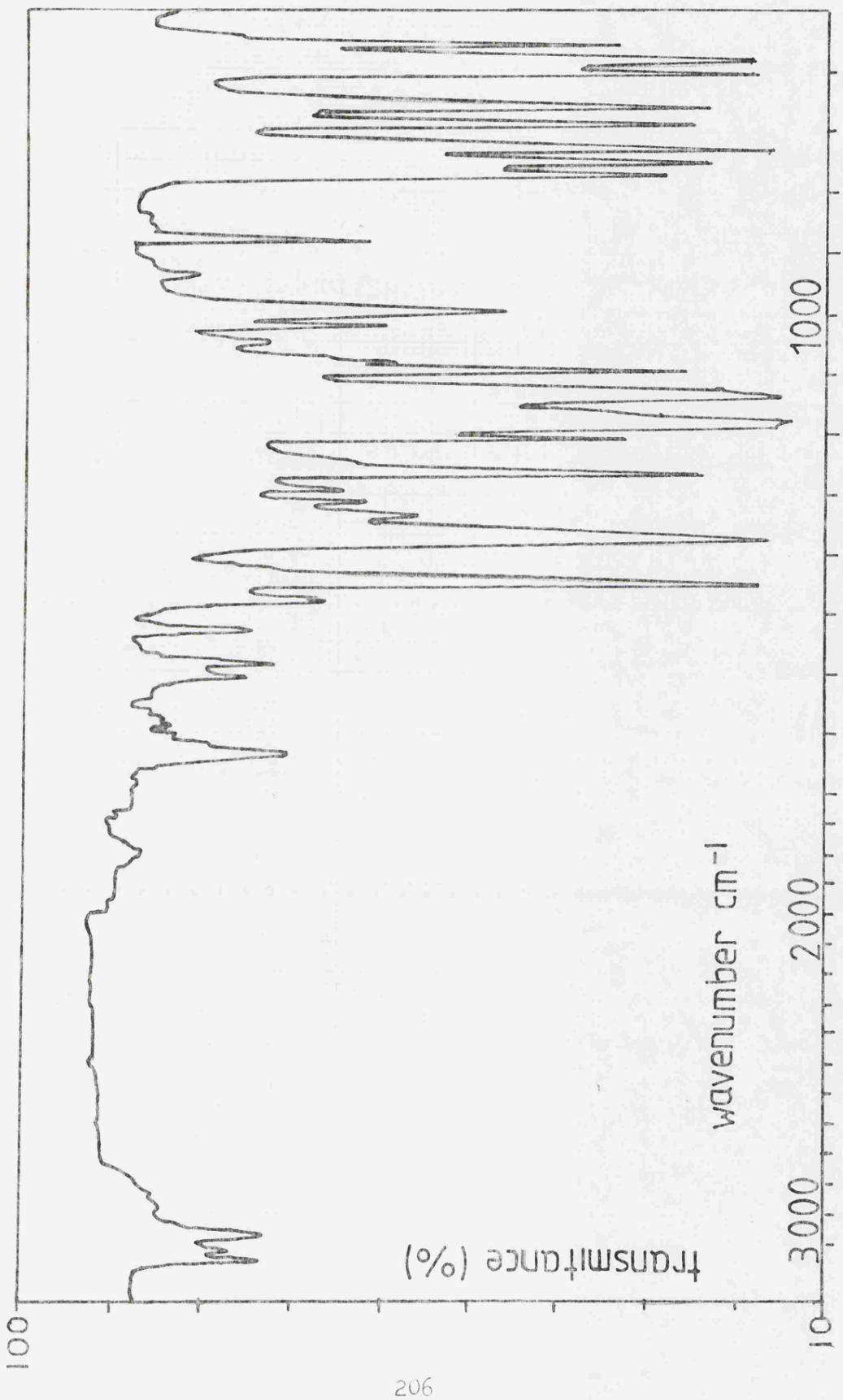

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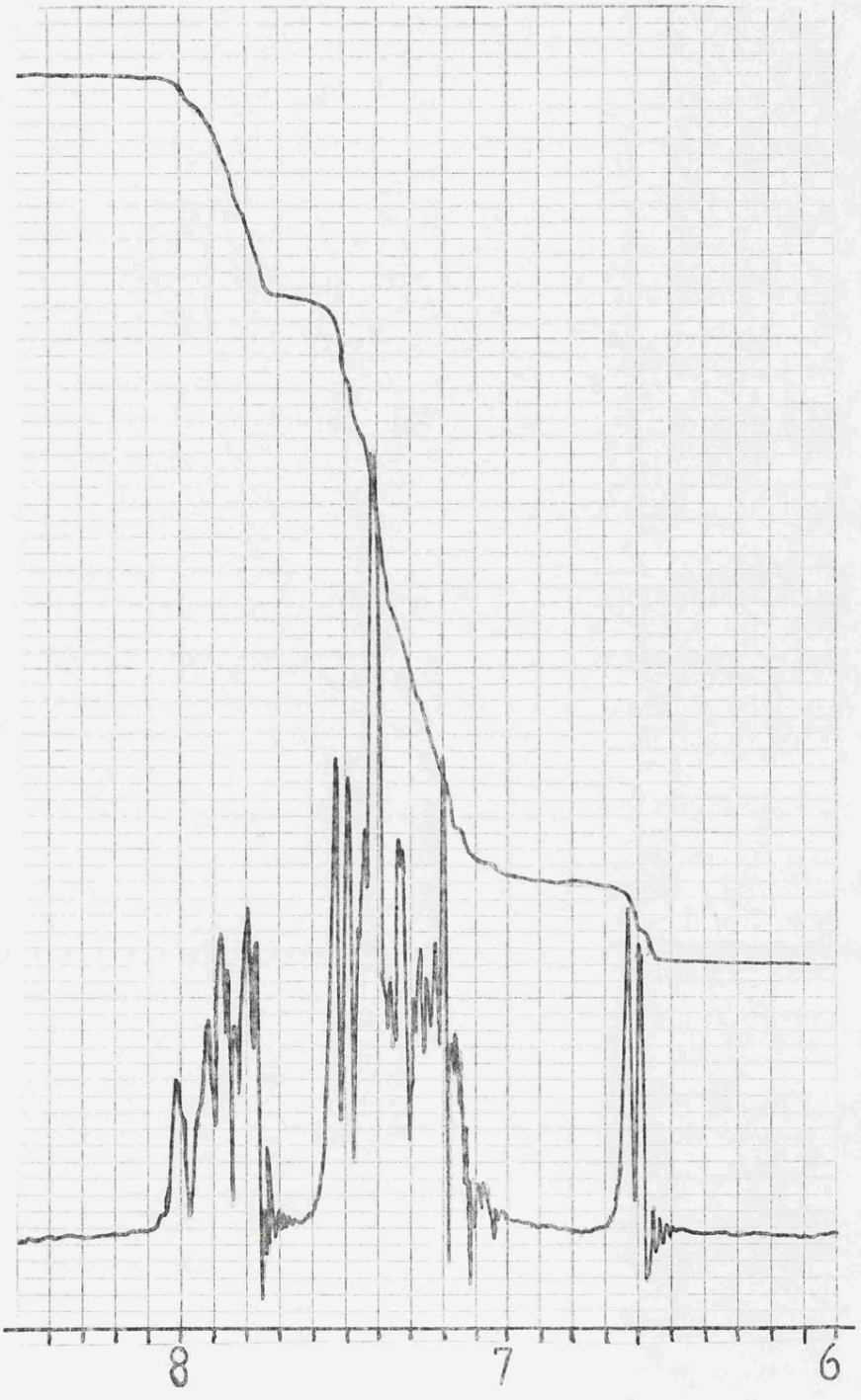

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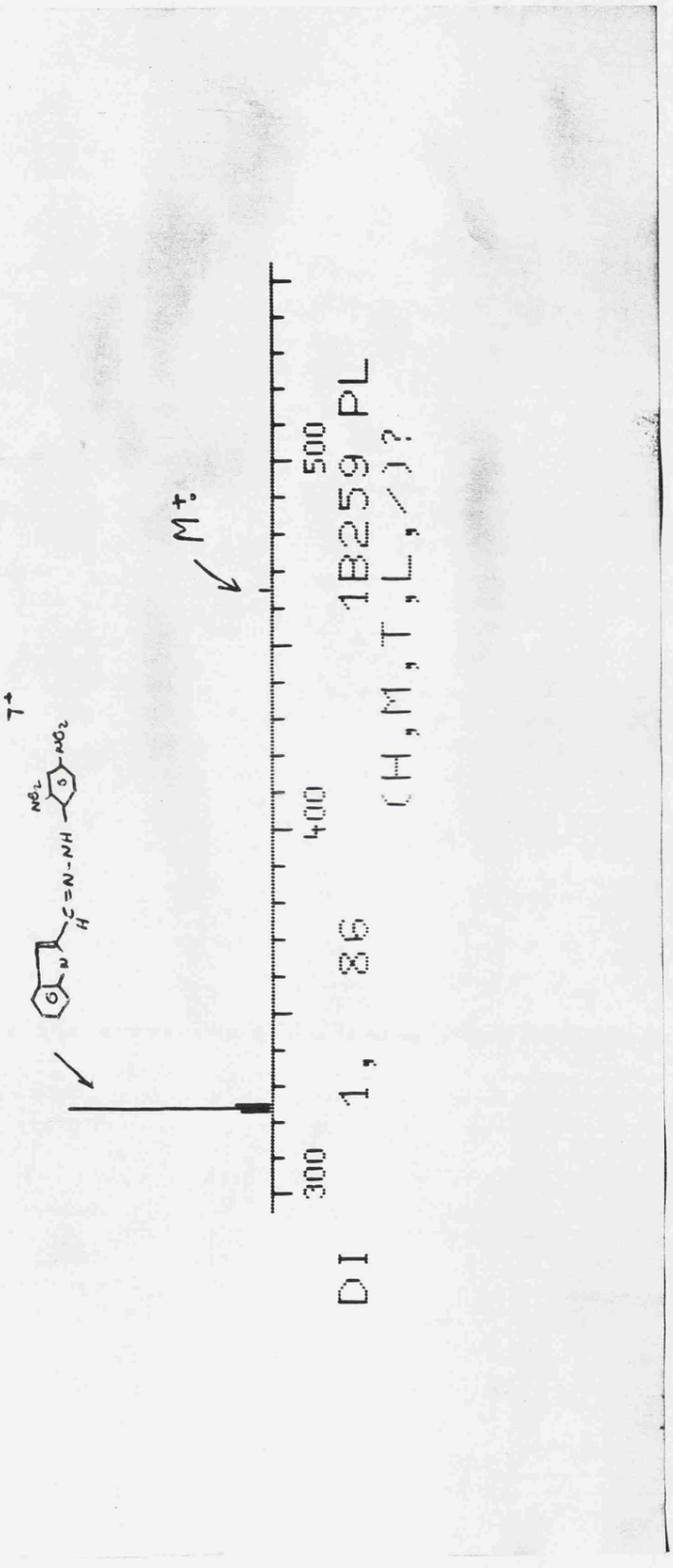

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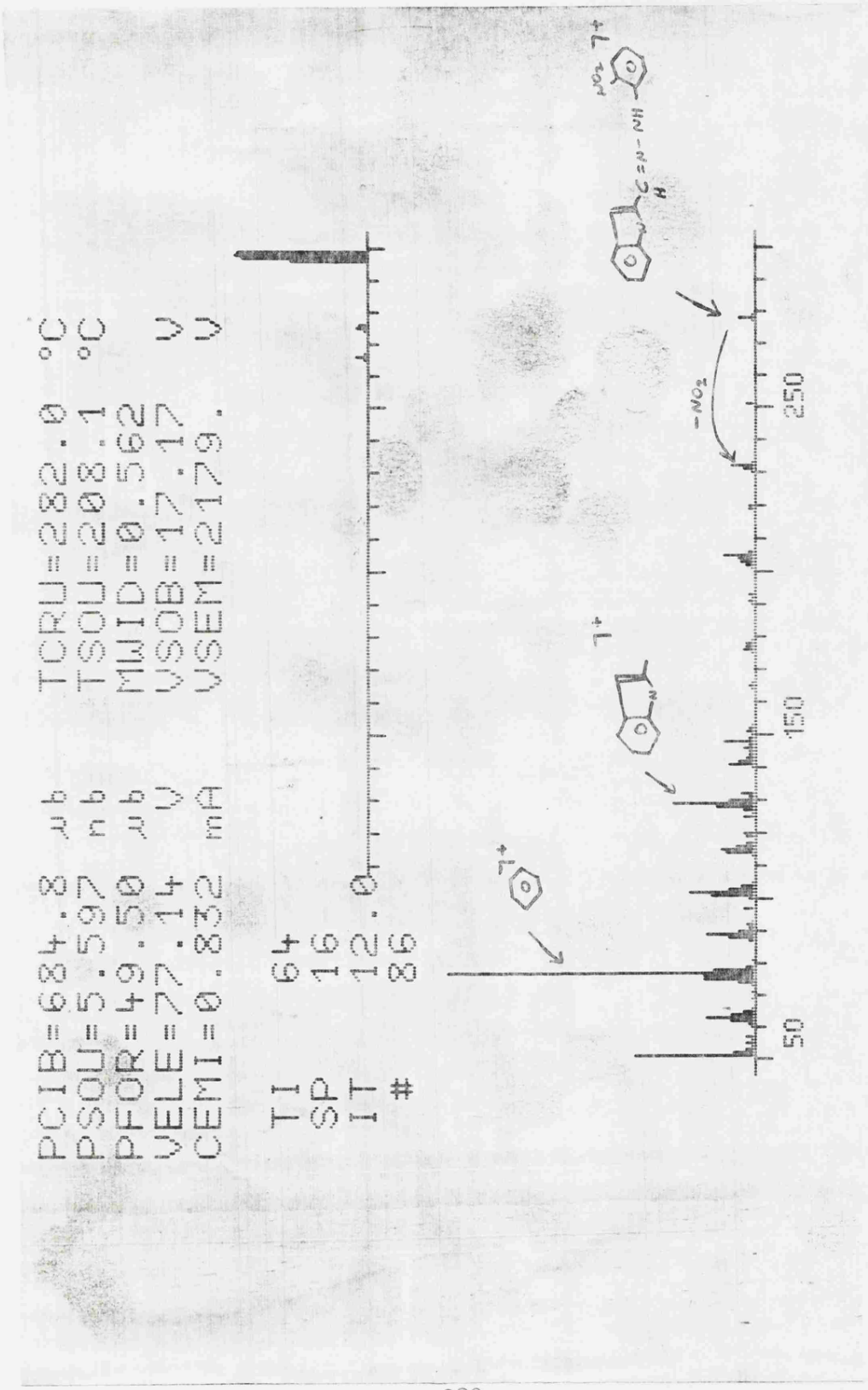
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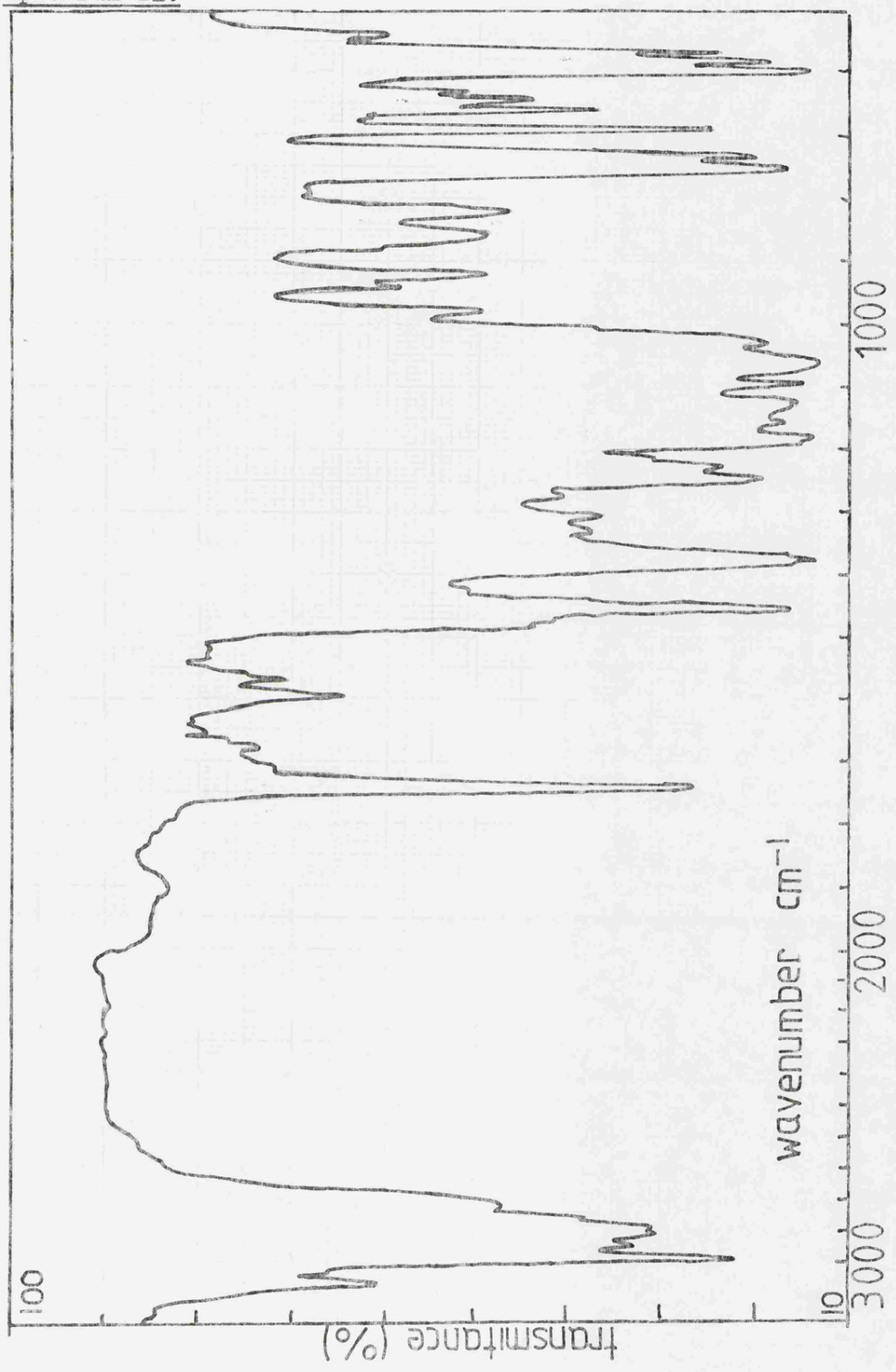

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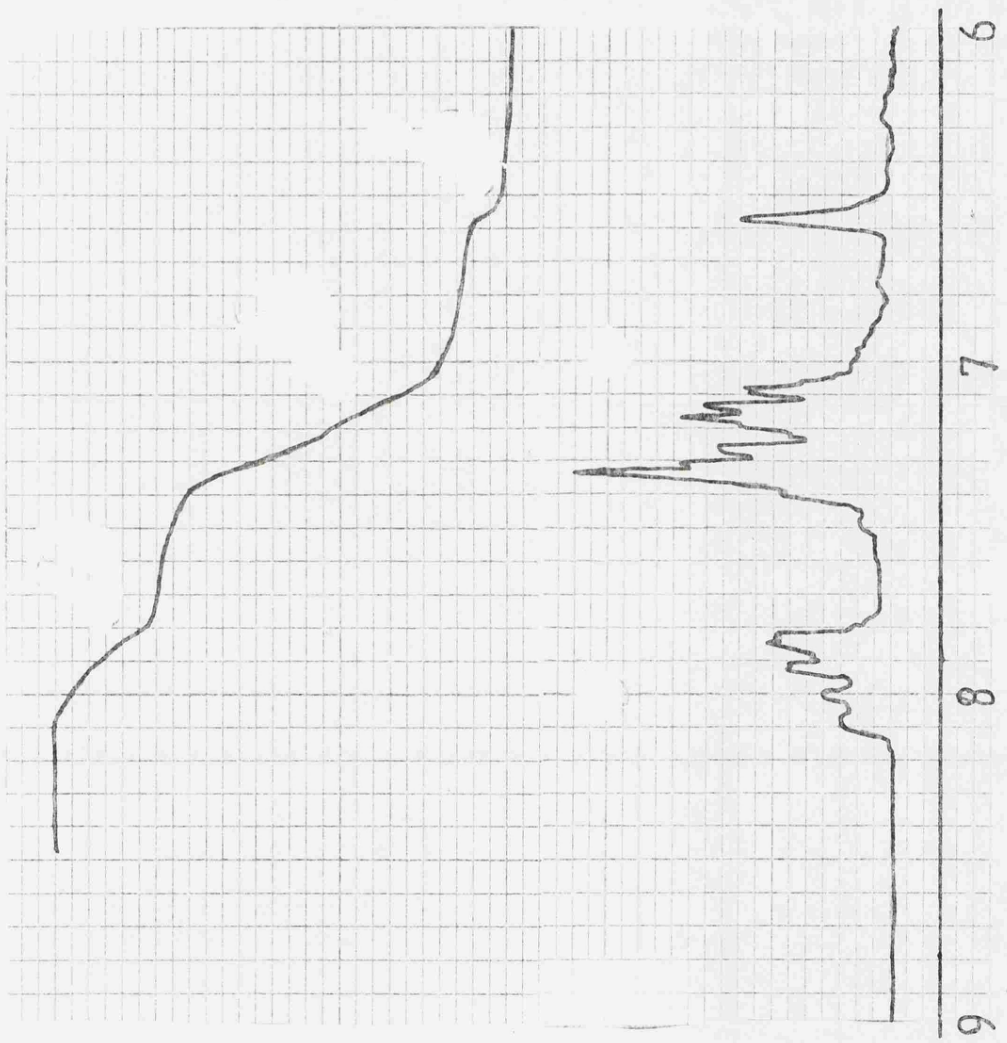

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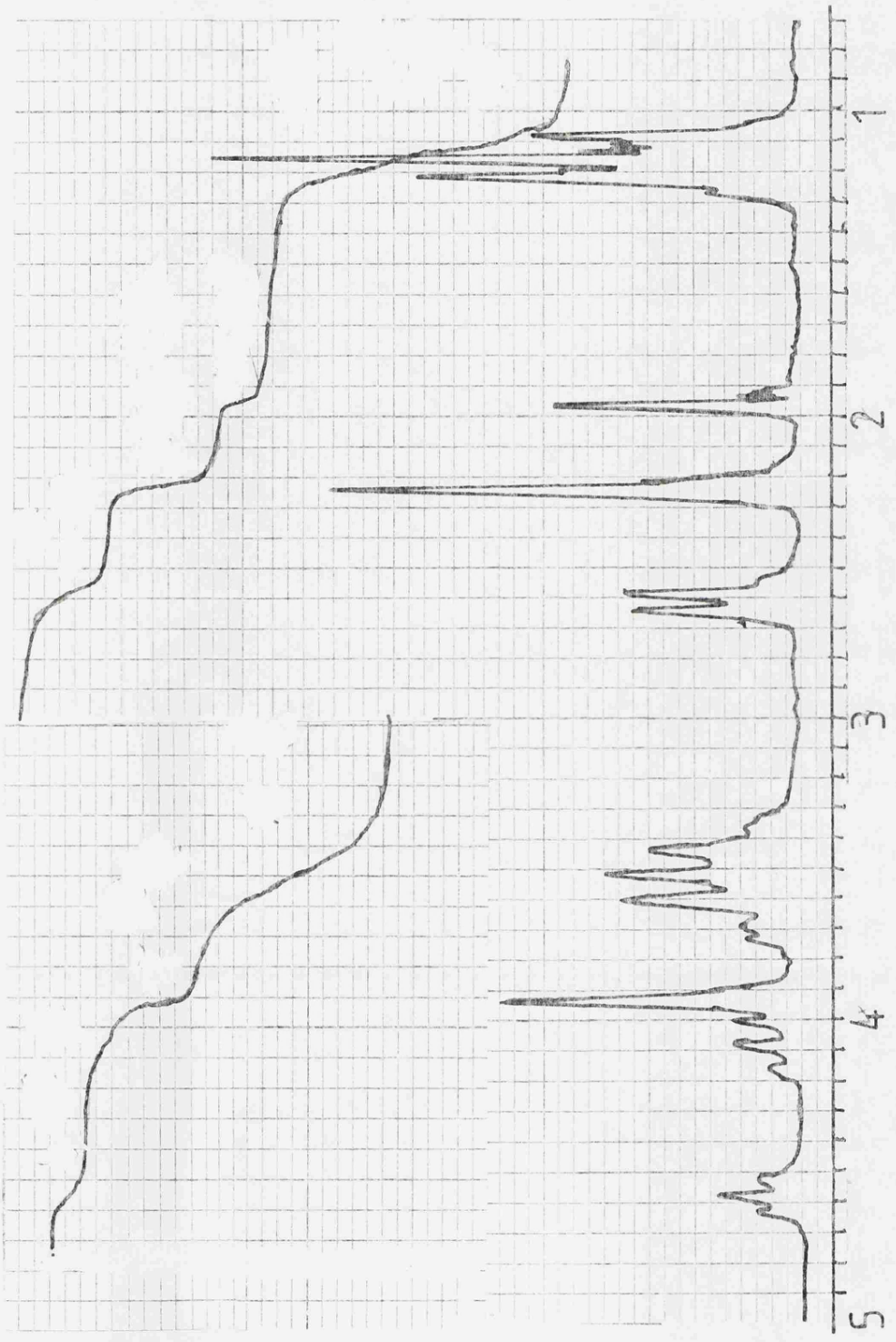

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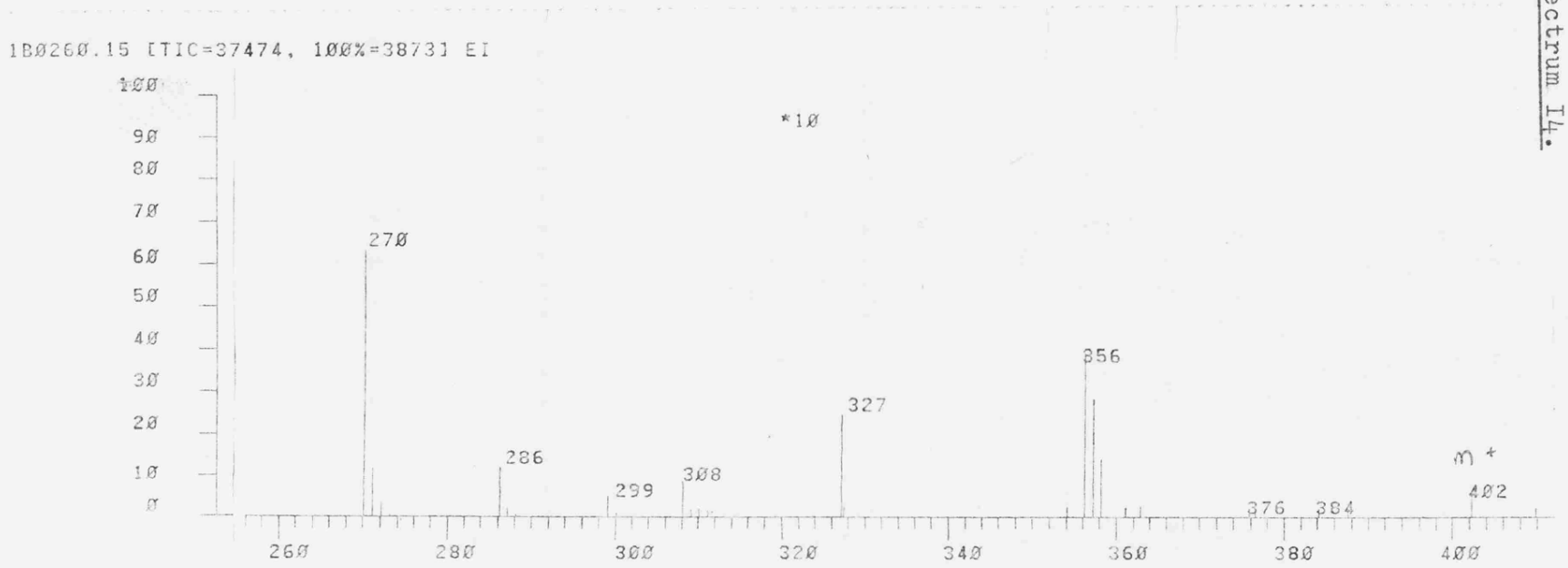
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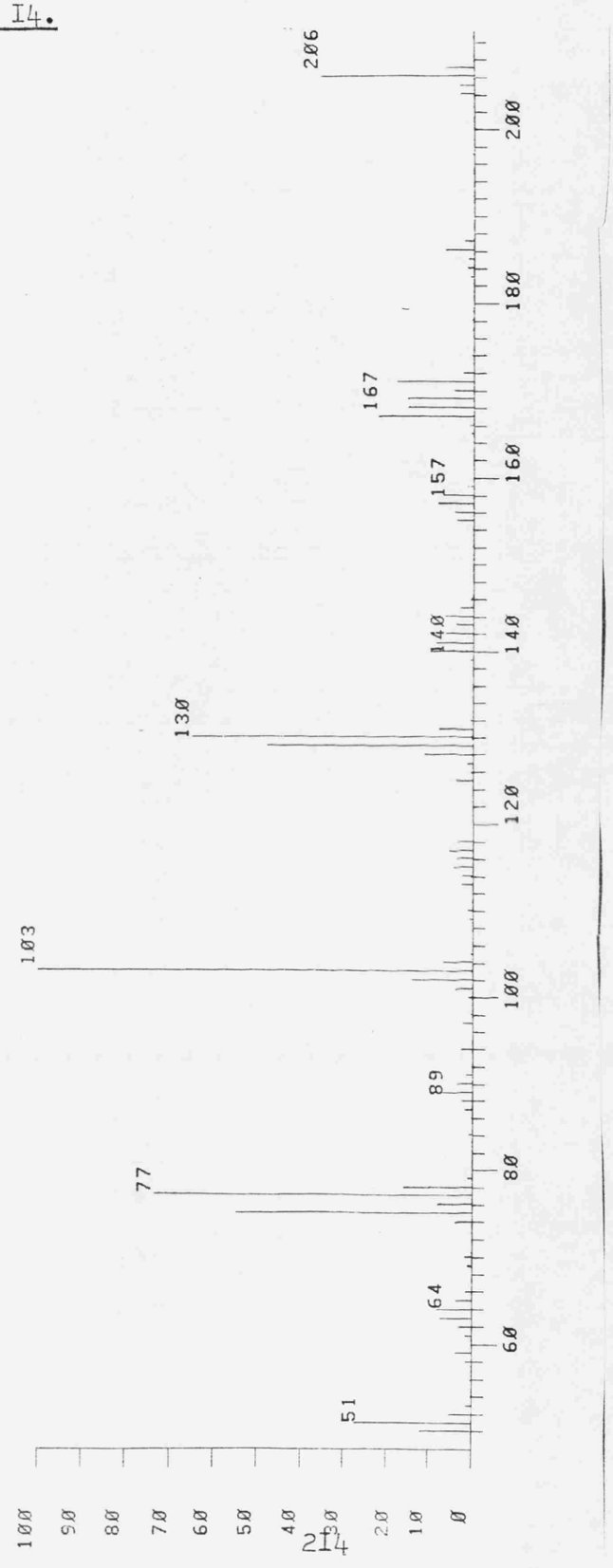
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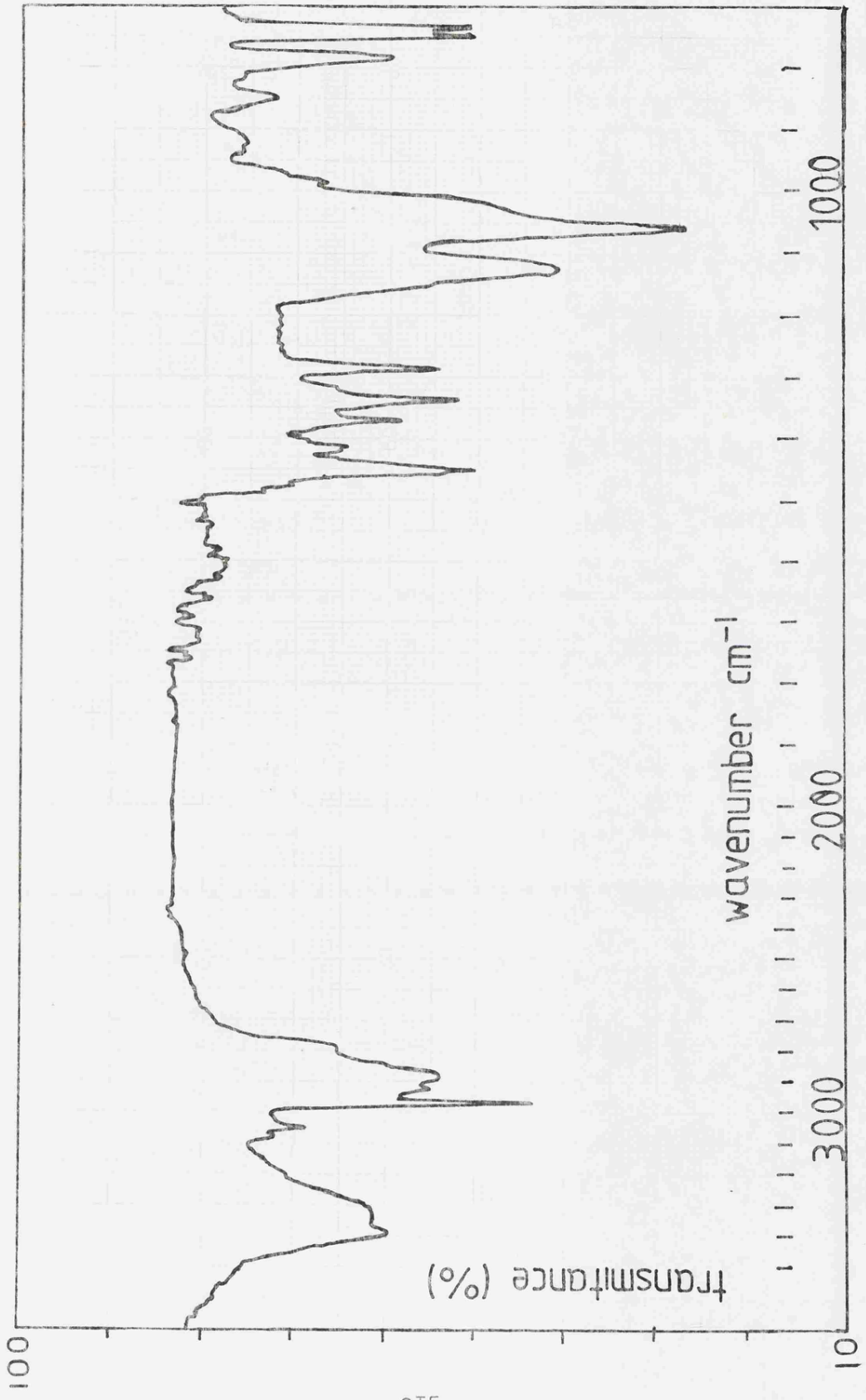

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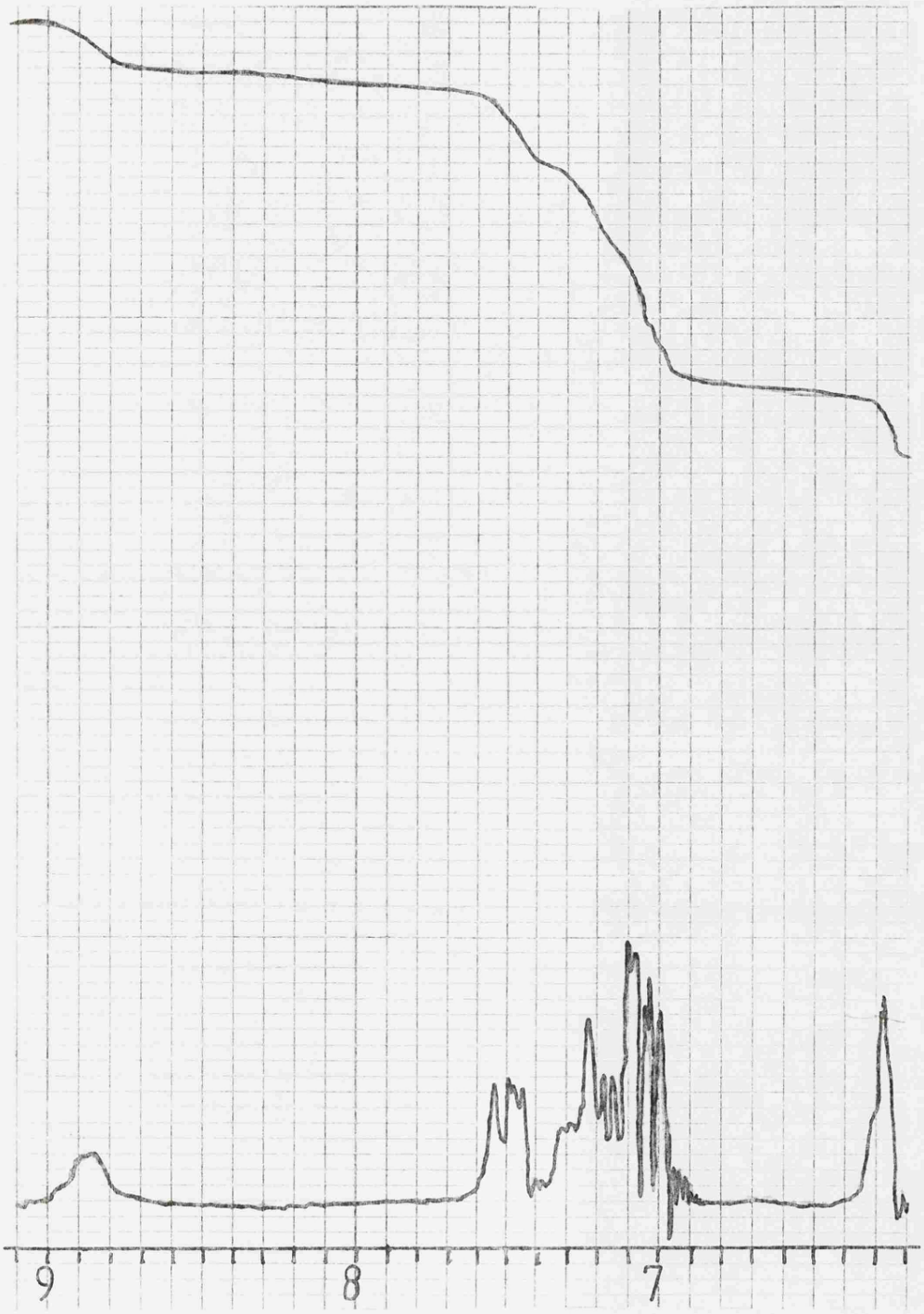

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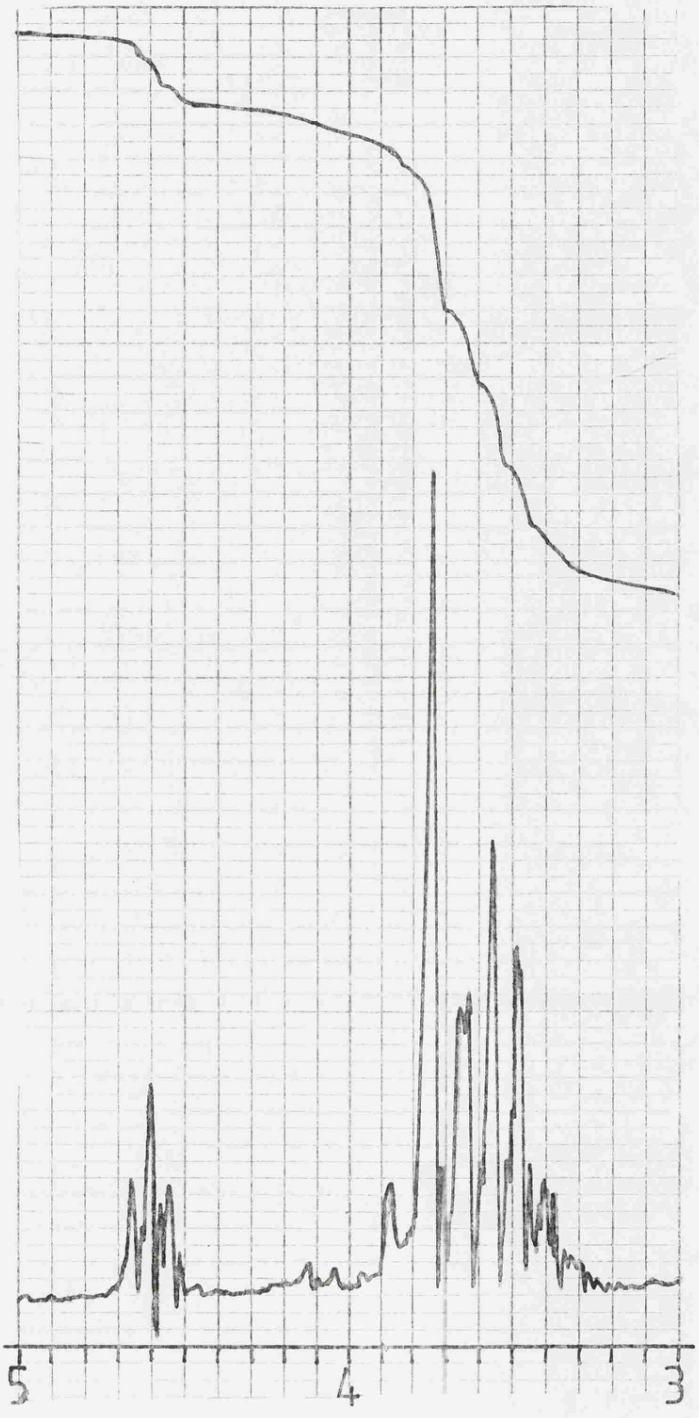

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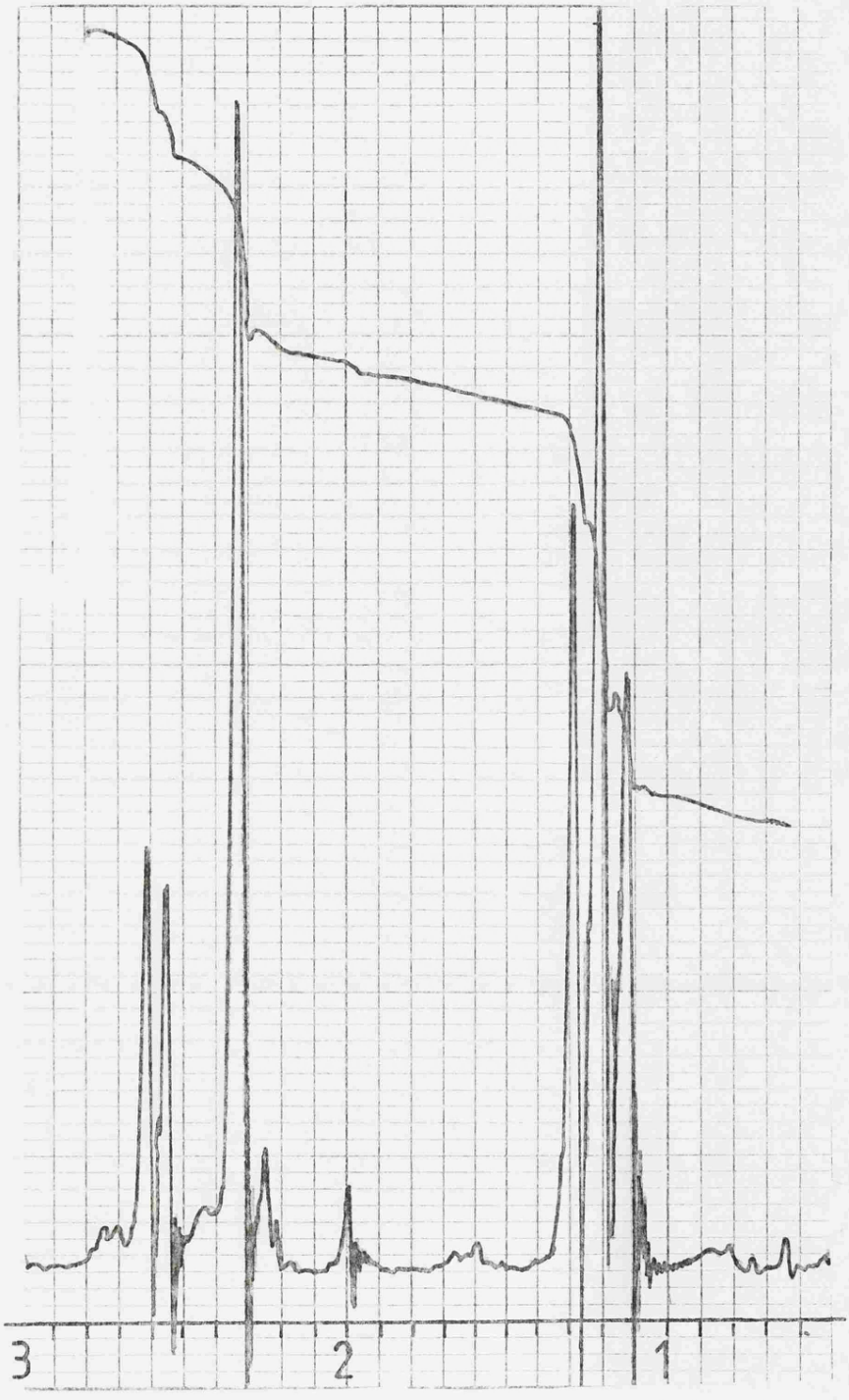

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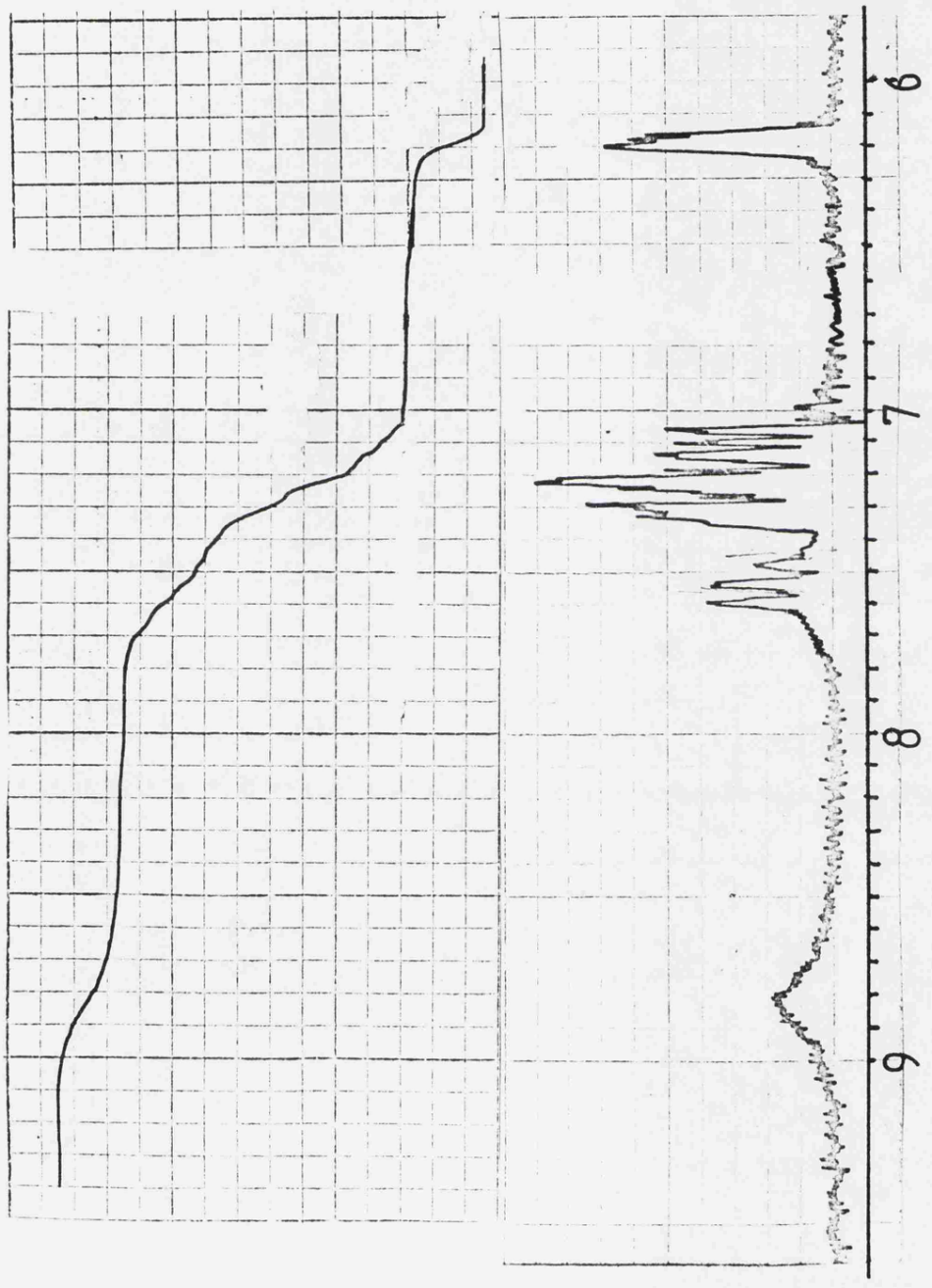

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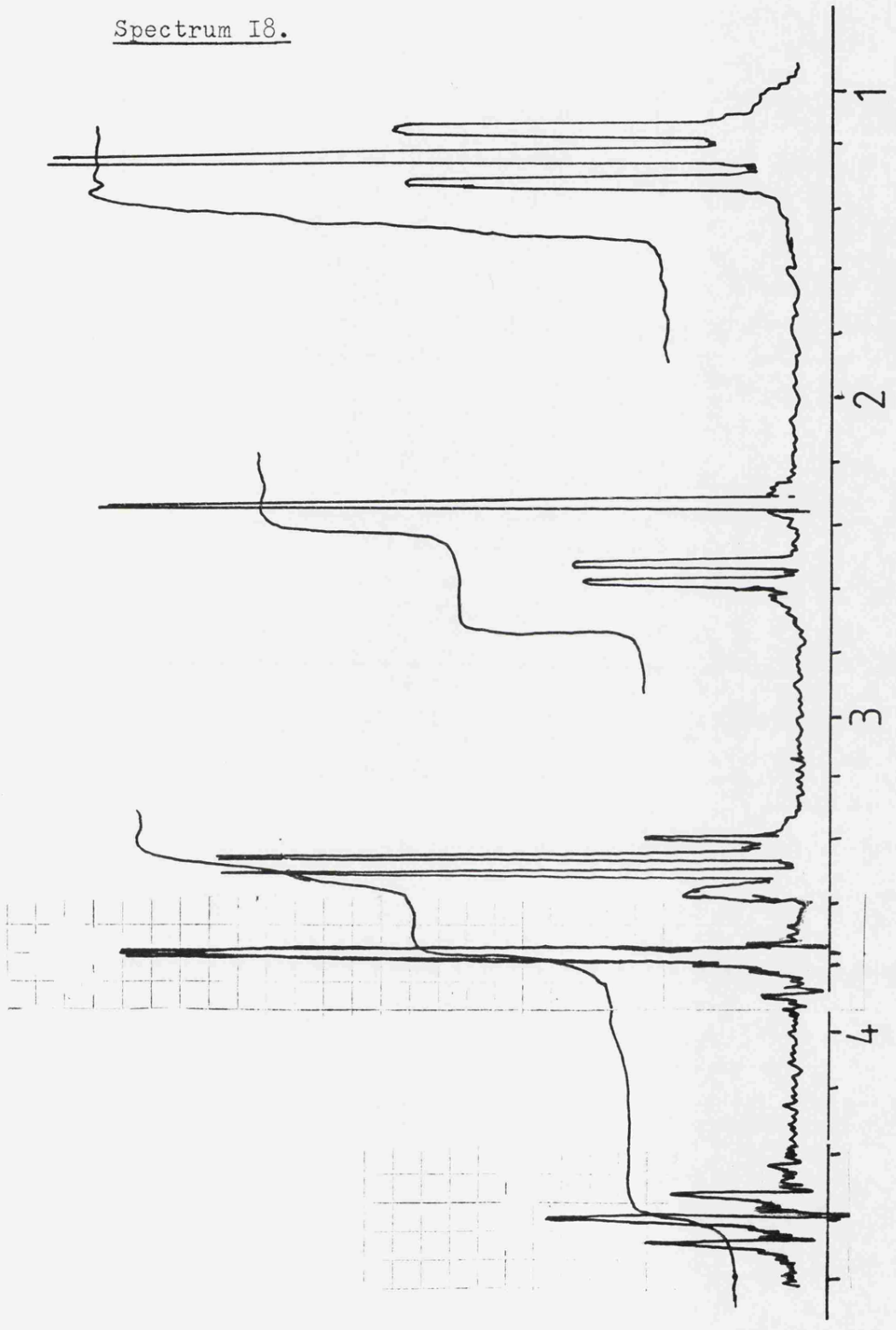

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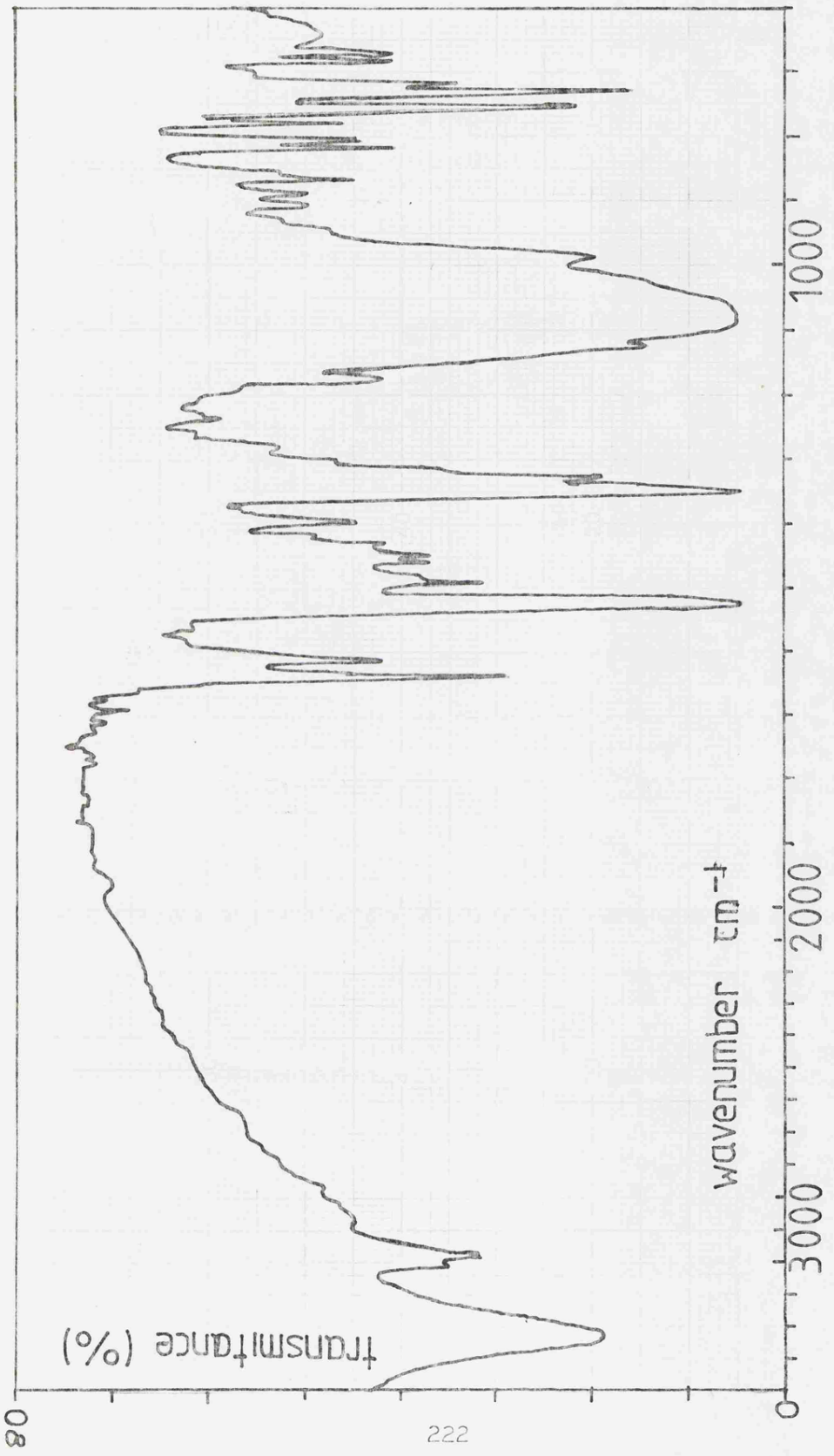

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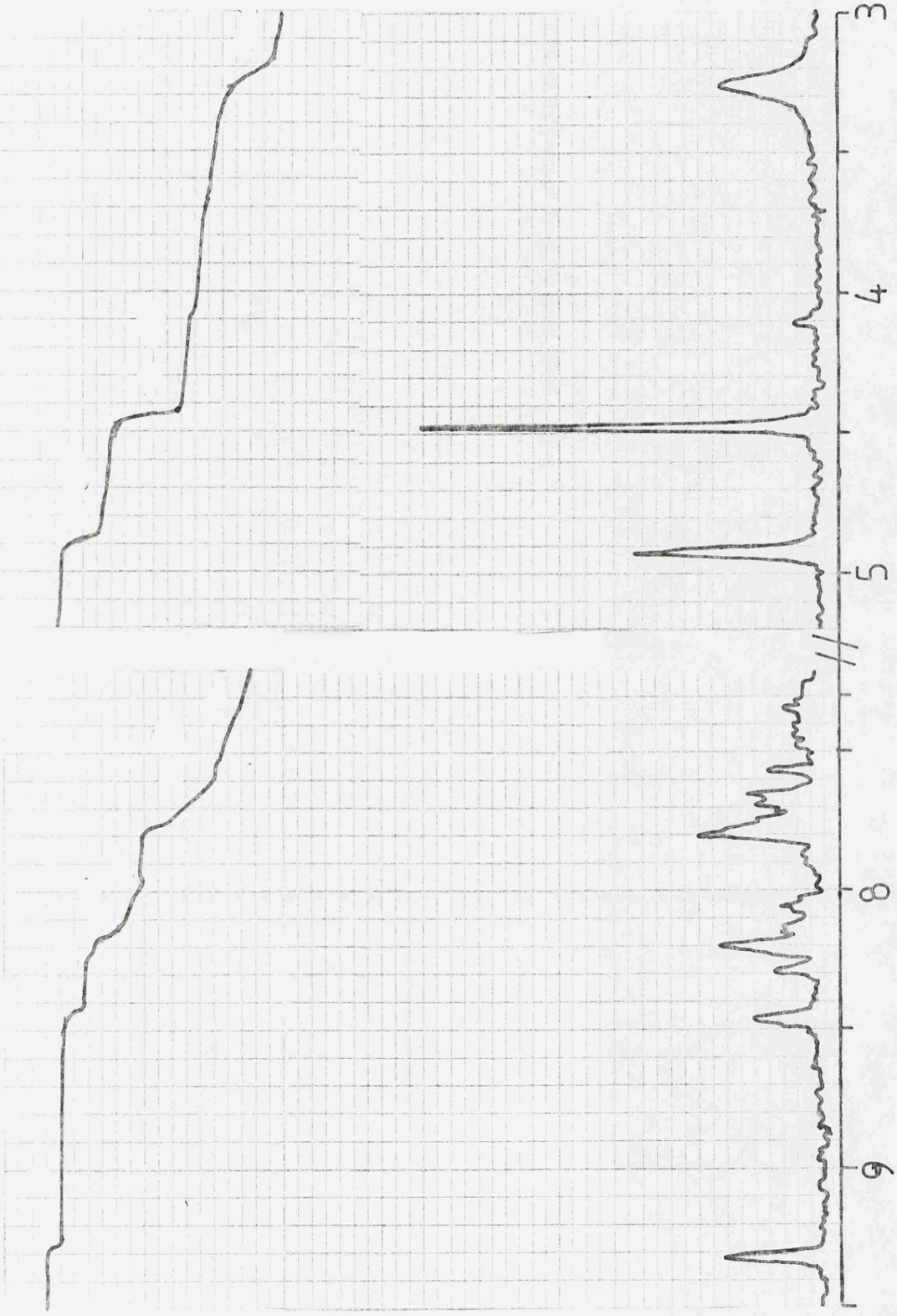

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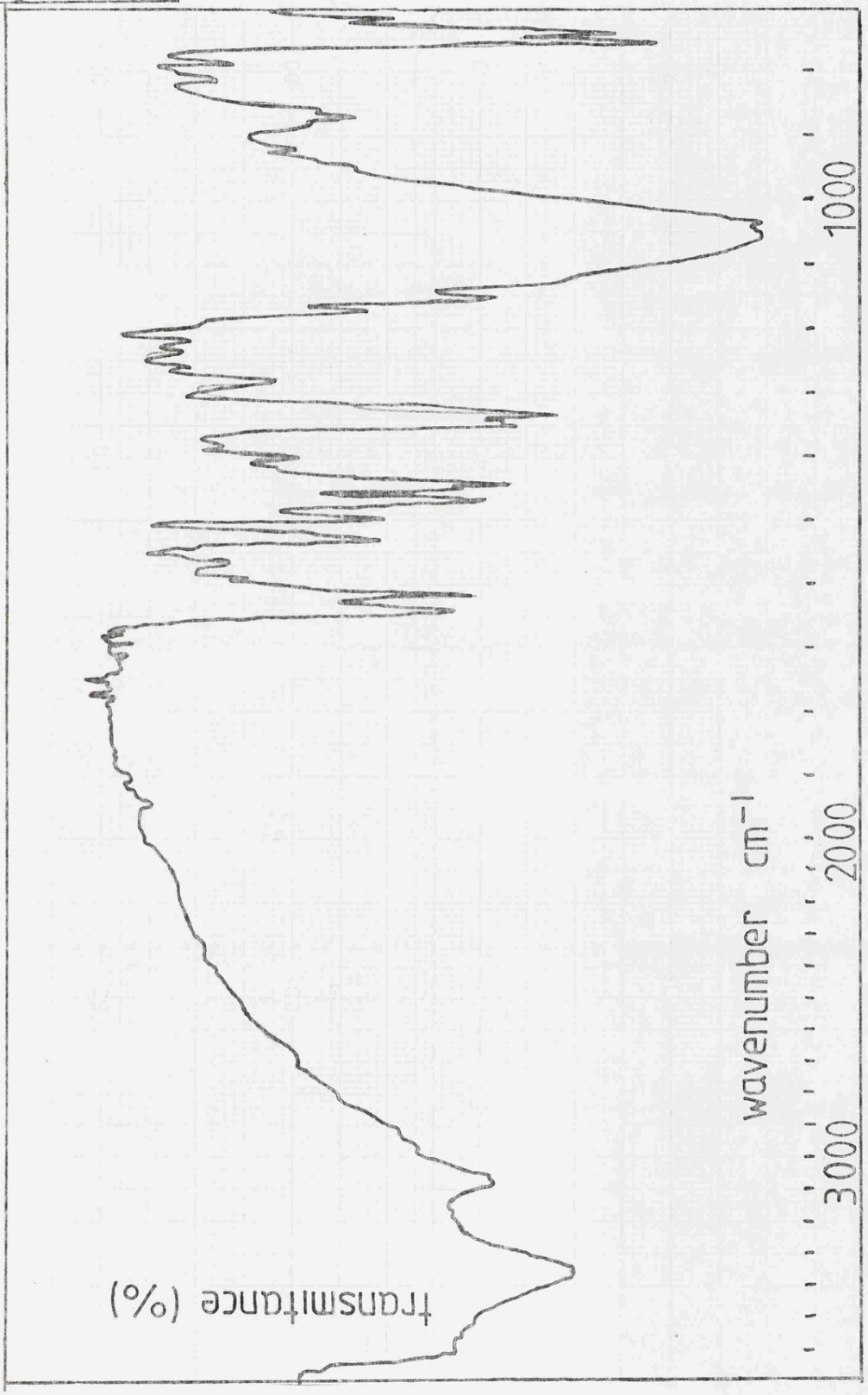

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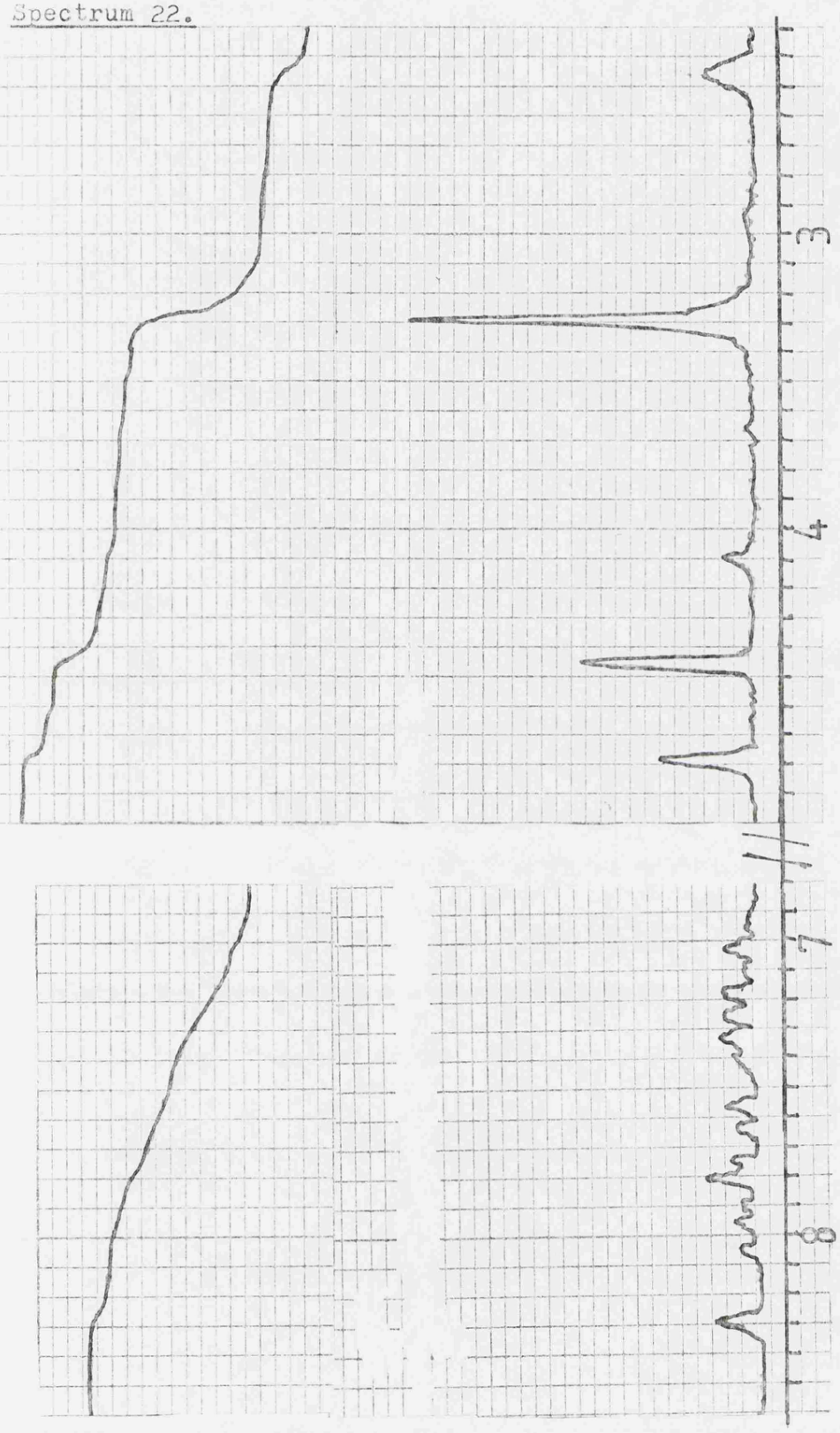

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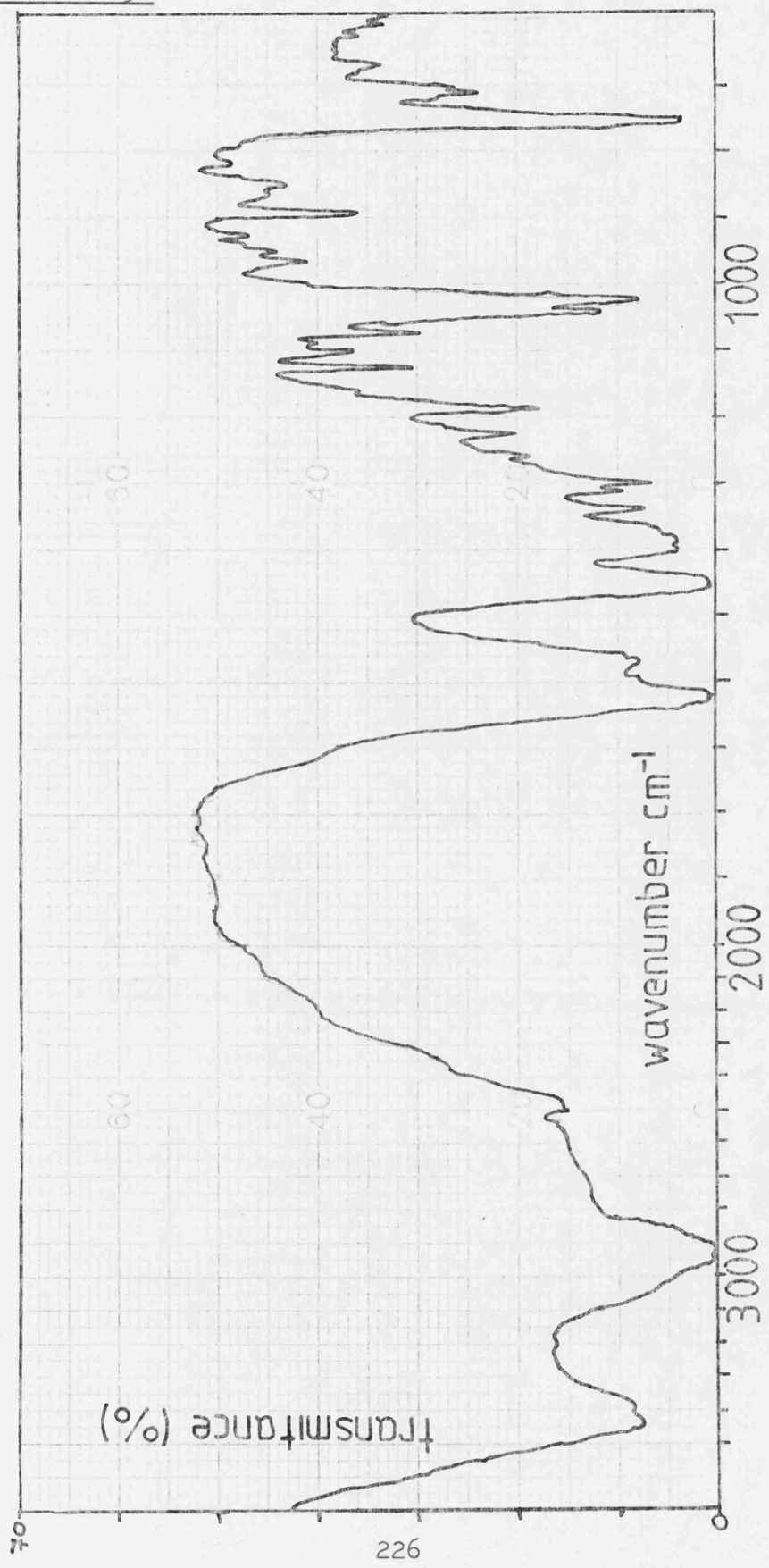
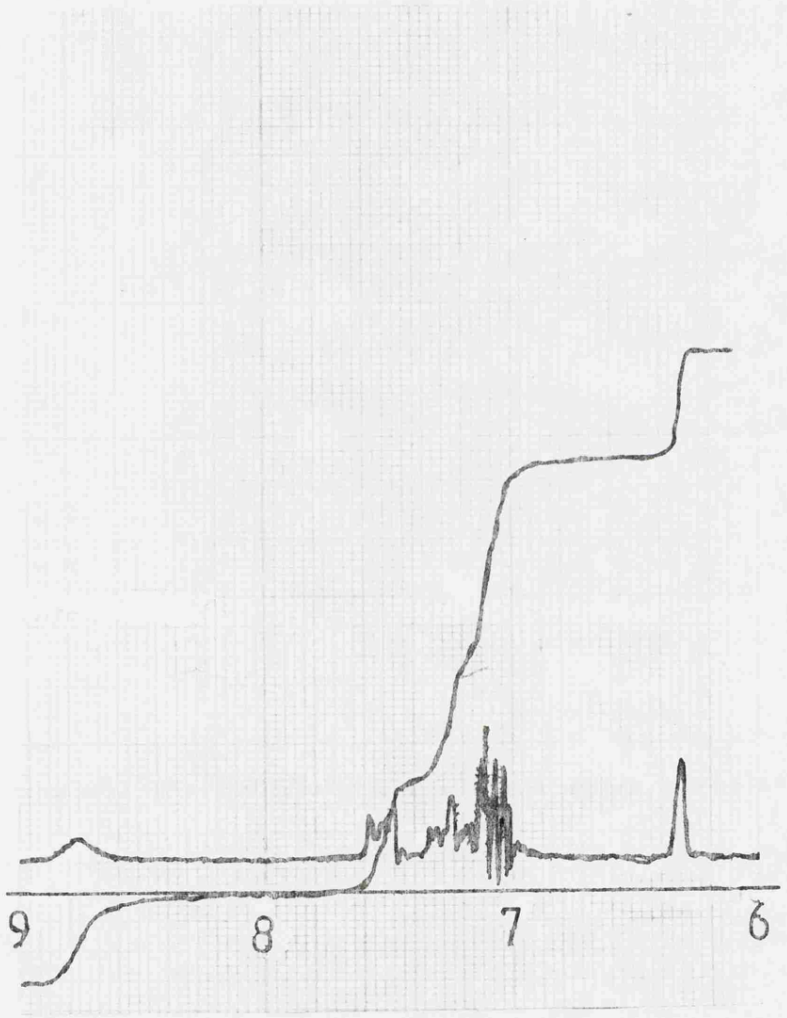
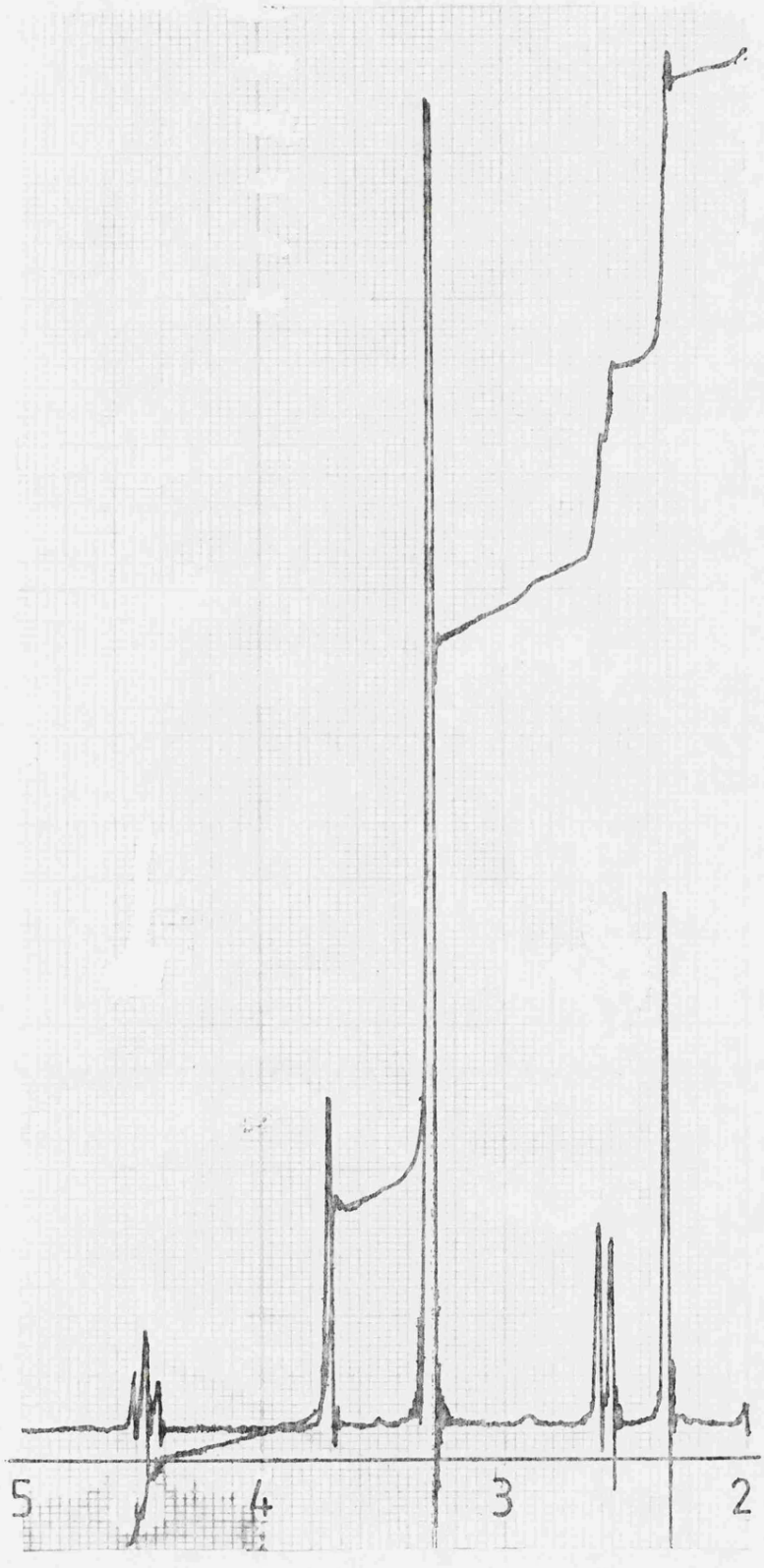

transmittance (%)
100
80
60
40
20
0
3000
2000
1000
wavenumber cm⁻¹

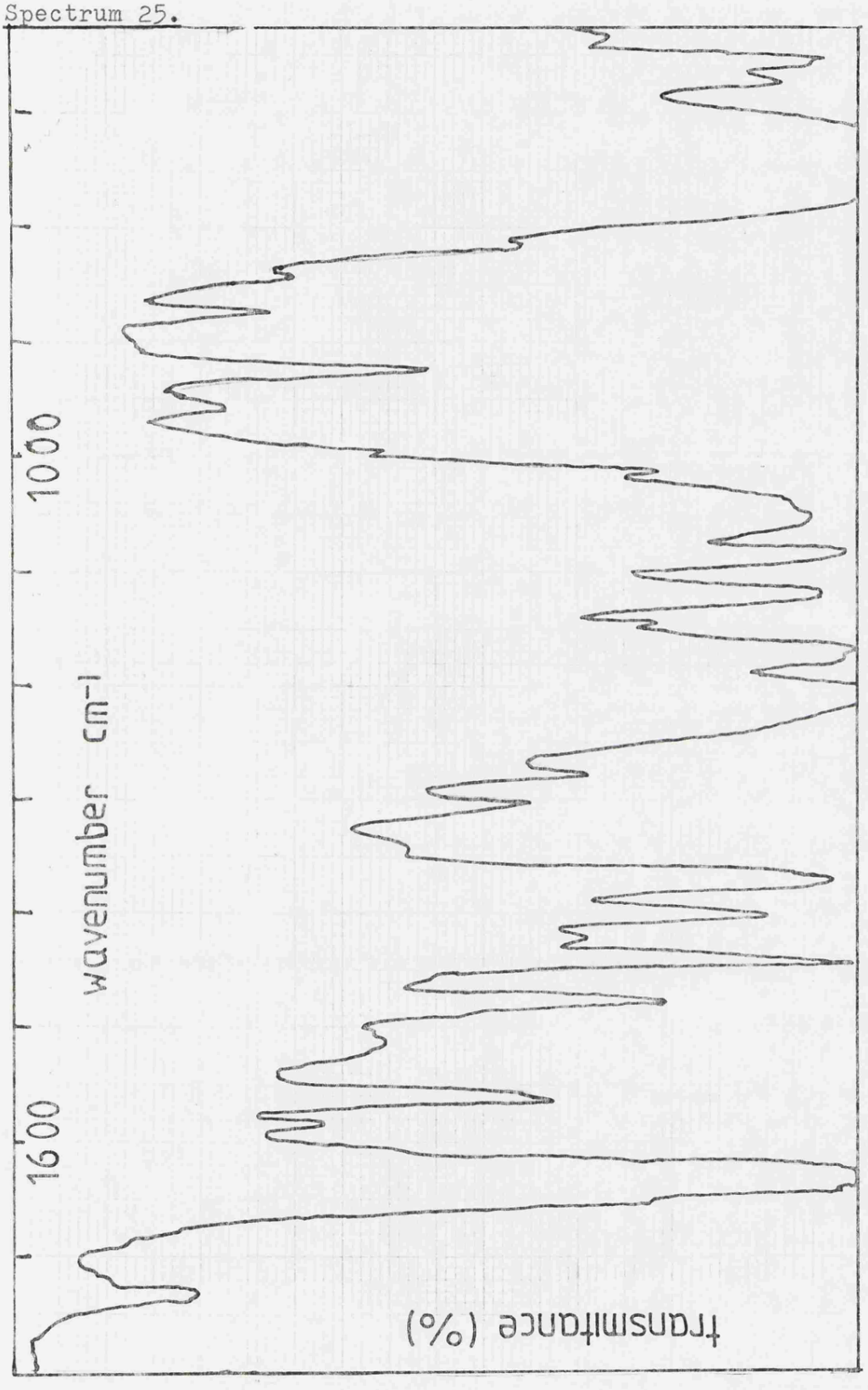
Spectrum 24.



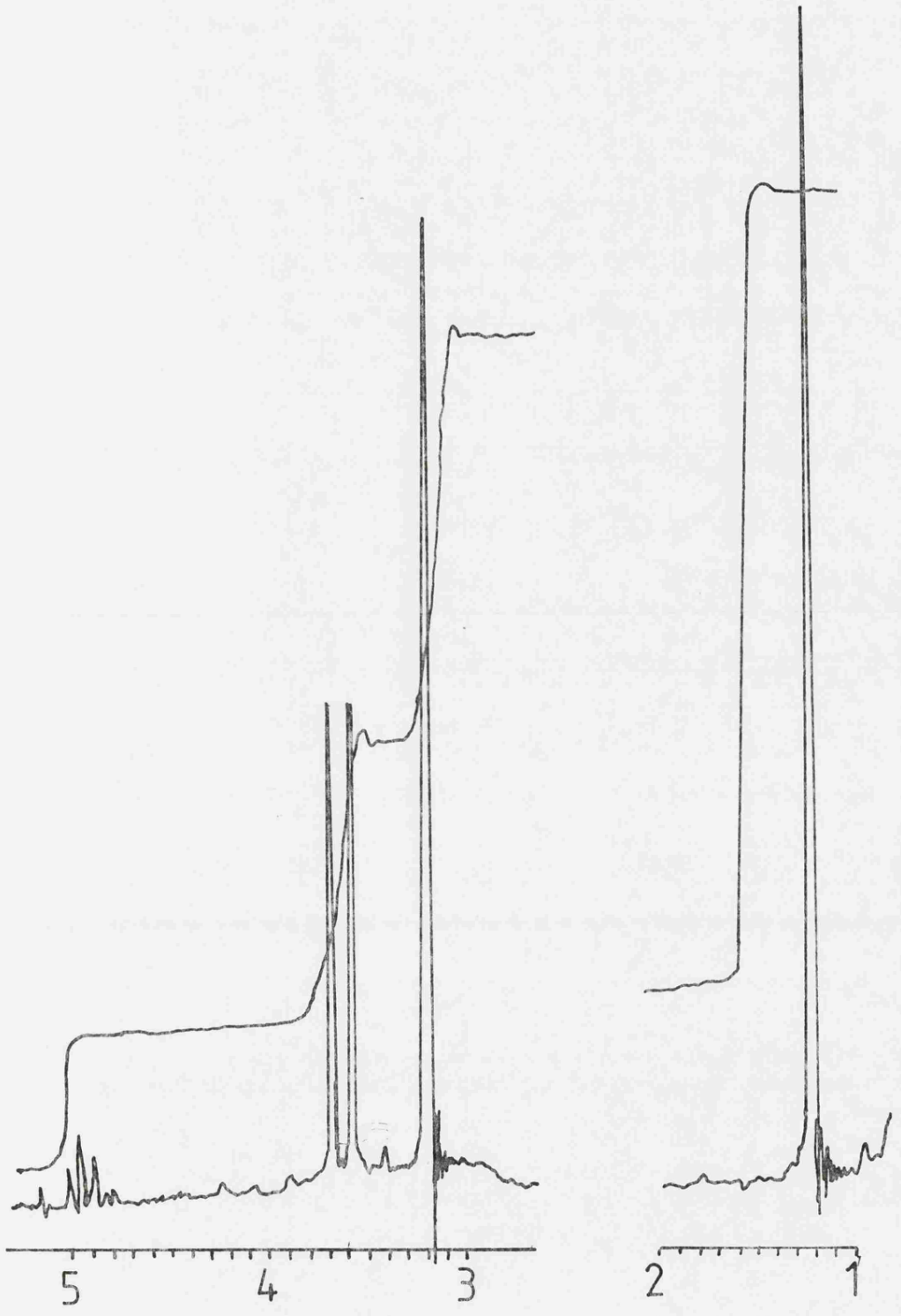
Spectrum 24.



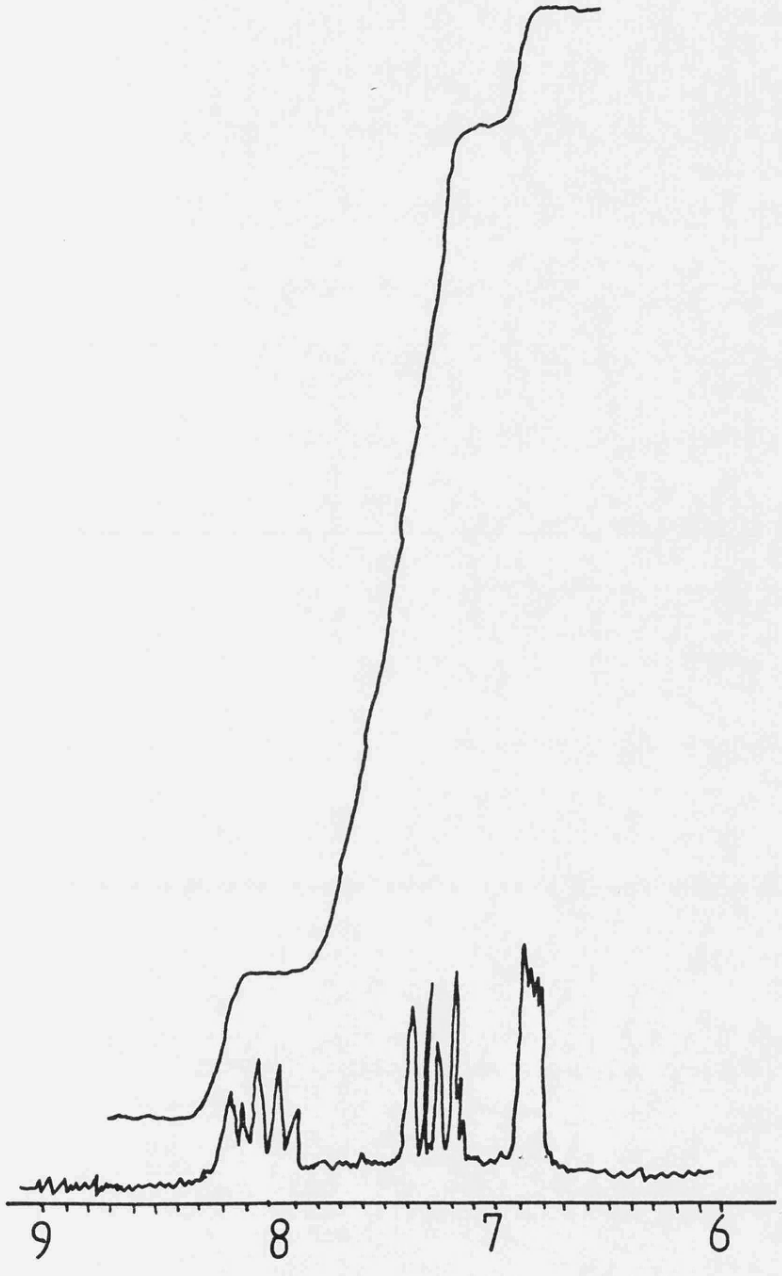
Spectrum 25.



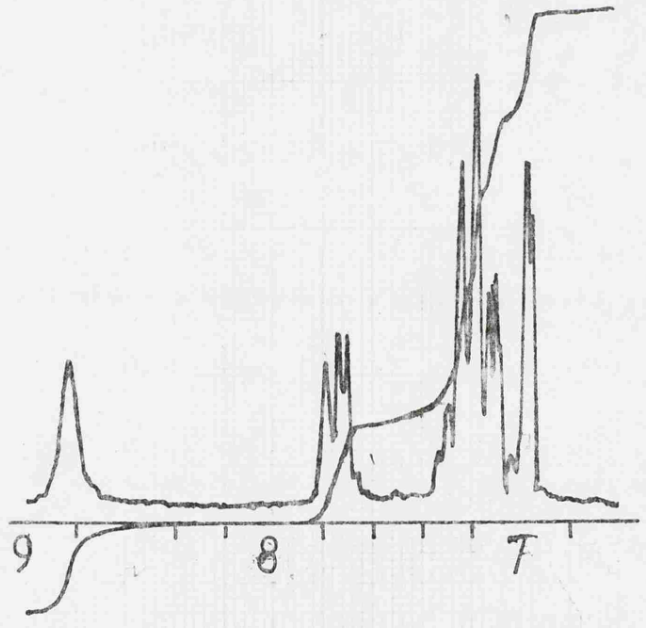
Spectrum 26.



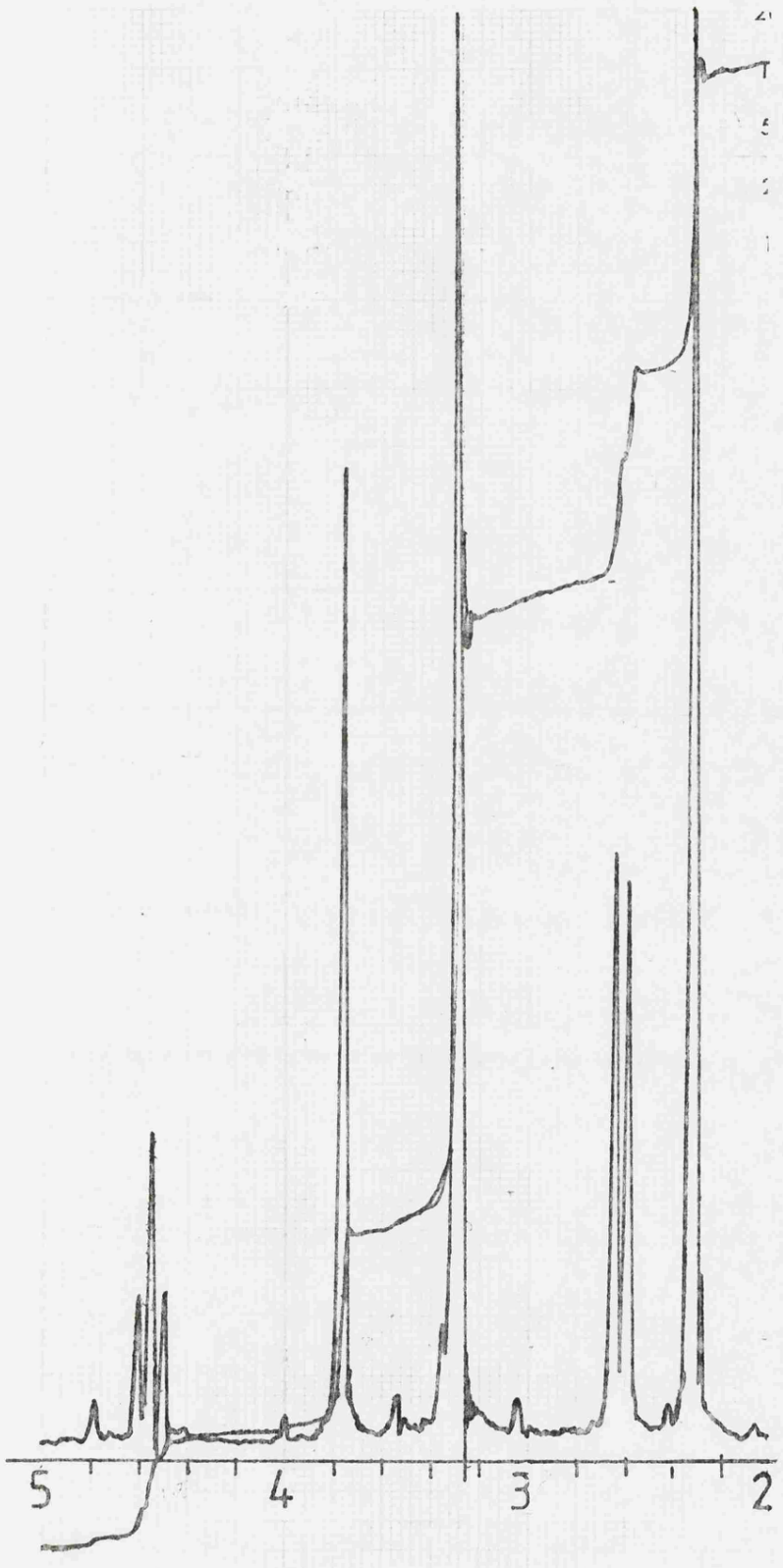
Spectrum 26.



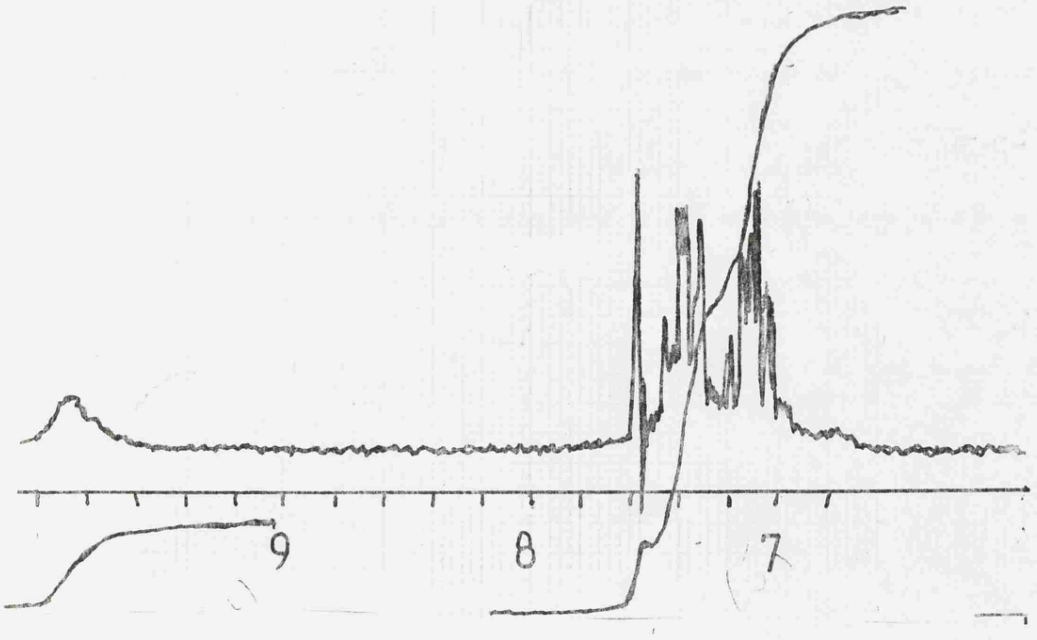
Spectrum 27.



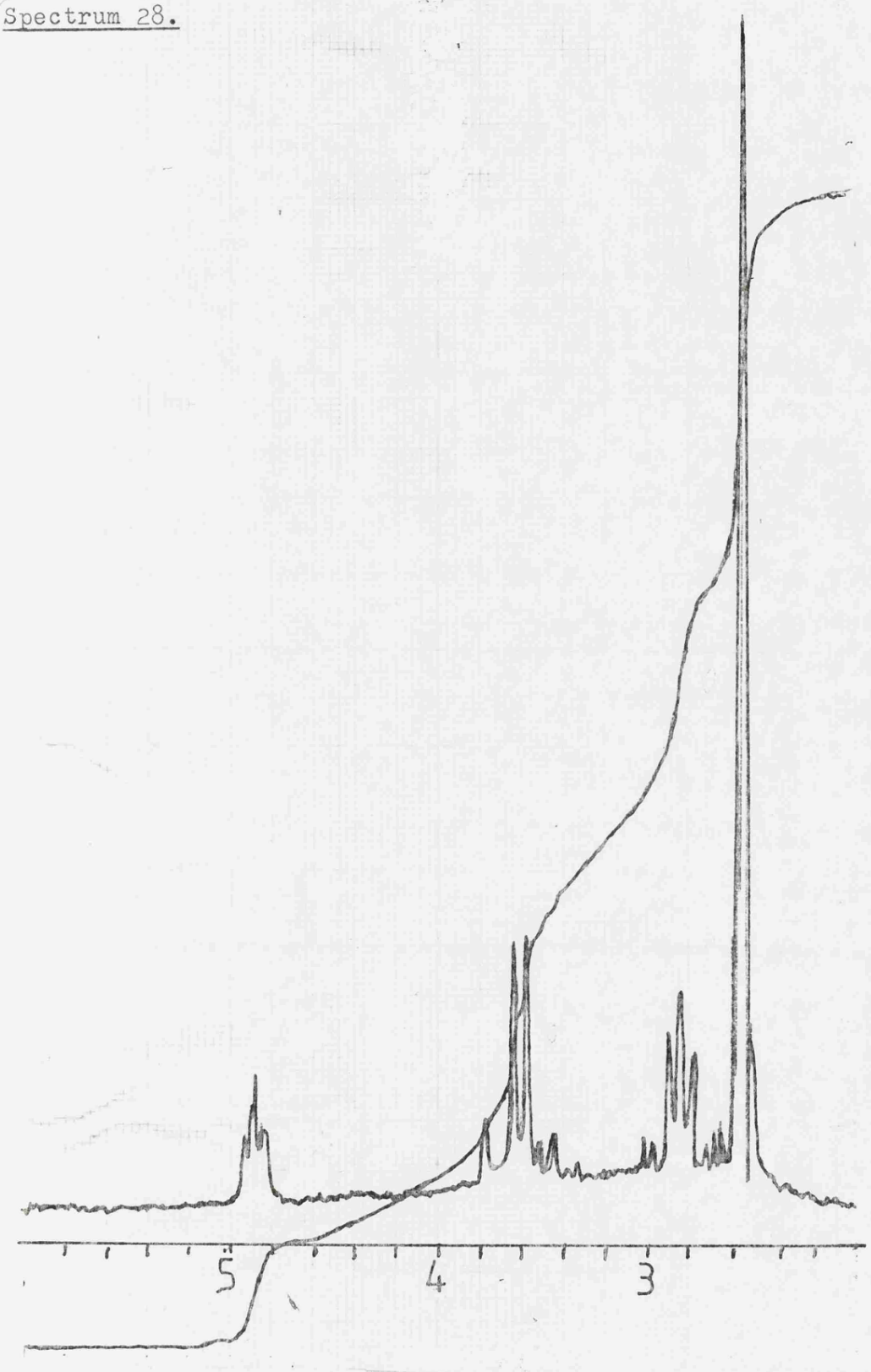
Spectrum 27.



Spectrum 28.



Spectrum 28.



APPENDIX II

β-Carboline Derivatives from an Aminoacetaldehyde Dimethylacetal.

K.A.Curness and S.F.Dyke

Heterocycles, I2(9), II33-II35 (I979)

HETEROCYCLES, Vol.12, No.9, 1979

β-CARBOLINE DERIVATIVES FROM AN AMINOACETALDEHYDE DIMETHYLACETAL

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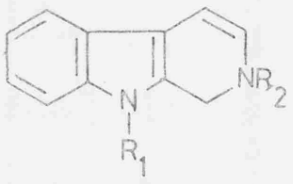
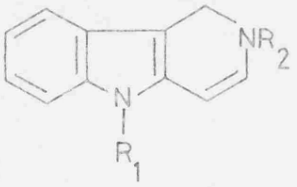
Abstract - Cyclisation of the acetal (3) with dilute HCl gave the hydroxy-β-carboline (8), and not the hydroxy-γ-carboline (4), as previously reported.

As part of a programme on the synthetic utility of cyclic enamines, we wished to prepare the dihydrocarbolines (1) and (2). From our experience with 1,2-dihydroisoquinolines[1,2] we anticipated that these β- and γ-carboline derivatives might be unstable, but would, nevertheless, exhibit useful enamine properties.



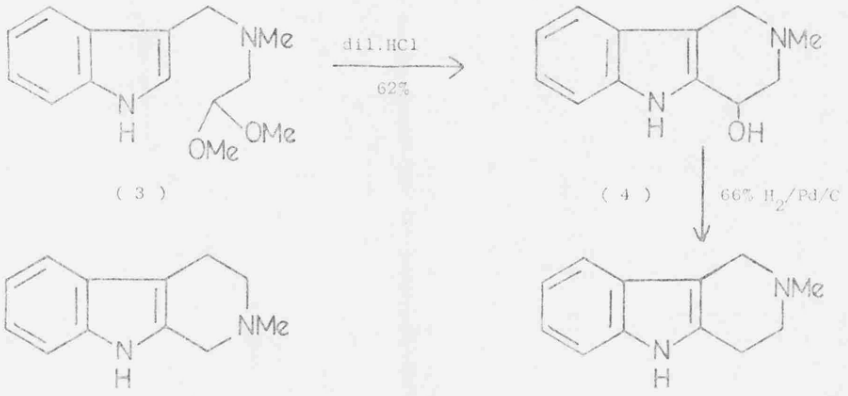
(1)



R_1, R_2 = H or alkyl (2)

Bobbitt, et al[3] have recently described the preparation of (3), m.p. 79-80°, by the Mannich condensation between indole, formaldehyde and N.methylaminoacetaldehyde dimethylacetal, and the conversion of it with dilute HCl into the γ-carboline derivative (4), m.p. 205-206°. No spectral data were recorded for (3) or (4), but the structure of (4) depended upon the fact that hydrogenolysis of it gave the known[4] N.methyl-1,2,3,4-tetrahydro-γ-carboline (5), m.p. 172-173°, although a direct comparison with an authentic specimen was apparently not carried out.

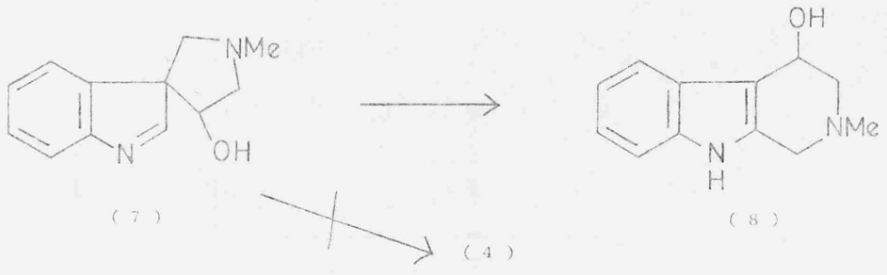
We, too, have carried out this sequence of reactions[5] but, interestingly, with different results. Our sample of (3), m.p. 77-78° [^{1}H NMR ($CDCl_3$), δ 8.84 s [1]; 7.74 m [1]; 7.34-7.08 m [3]; 6.93 d, J = 2 Hz [1]; 4.56 t, J = 5 Hz [1]; 3.76 s [2]; 3.29 s [6]; 2.61 d, J = 5 Hz [2]; 2.32 s [3]] was treated with 6M HCl exactly as described by Bobbitt and we, too, obtained a hydroxycarboline derivative (52% yield) m.p. 202-203° [^{1}H NMR ($CDCl_3/d_6$ DMSO), δ 9.88 s [1];



(3) (4) (6) (5)

7.4-7.24 m [2]; 7.08-7.0 m [3]; 4.82 t, J = 5 Hz [1]; 3.80 d, J = 5 Hz [2]; 3.5 q, J = 14 [2]; 2.48 s [3]]. However, when this compound was reduced, either catalytically or with $LAH/AlCl_3$, the tetrahydrocarboline obtained (63% yield) had m.p. 215-216°[c], picrate m.p. 195-196°. This compound was found to be identical (mixed m.p. of the base and the picrate) with N,methyl-1,2,3,4-tetrahydro-β-carboline (6), prepared[4] by reduction of N,methyl-β-carbolinium iodide, and not with N,methyl-1,2,3,4-tetrahydro-γ-carboline (5), m.p. 170-171°, picrate m.p. 129-130°, also prepared by an independent route[6].

On one occasion when (3) was treated with dilute HCl, an intermediate was isolated, the spectral characteristics of which strongly supported the indolenine structure (7), although it could not be obtained analytically pure [^{1}H NMR ($CDCl_3$) δ 10.42 s [1]; 7.71 s [1]; 7.4-7.29 m [2]; 7.16-6.98 m [2]; 4.88 t [1]; 3.66 br s [2]; 2.86 dd, J = 12 Hz and 4 Hz [2]; 2.36 s [3]]. Such an intermediate could be anticipated[7] to rearrange to either the β- or the γ-carboline skeleta (8) or (4), respectively; in our case it was clearly the β-carboline (8) that was formed.



(7) (8) (4)

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5. We thank Professor Bobbitt for experimental details well before publication of his results.

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